

THE
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OF THE
MEDICAL SCIENCES

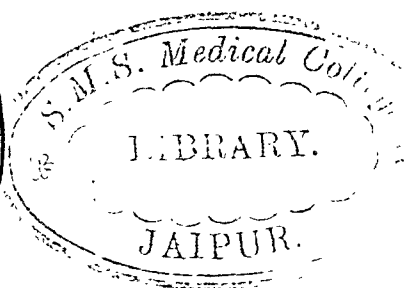
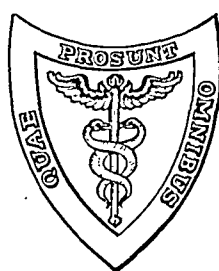
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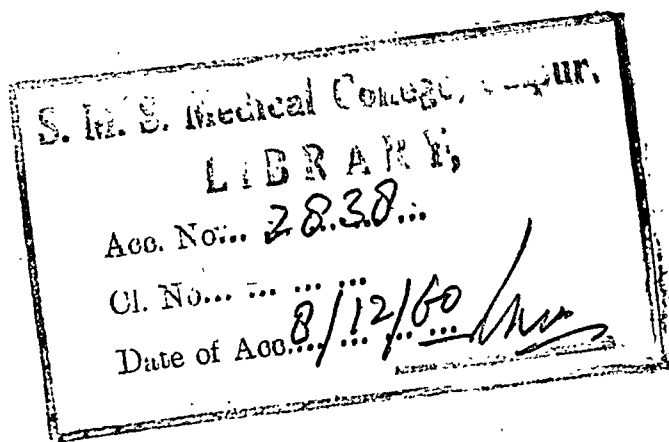
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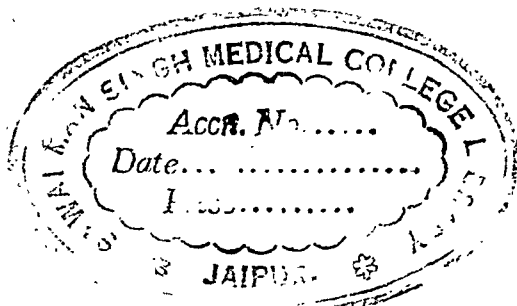
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ORIGINAL ARTICLES.

**METABOLIC STUDIES IN ADDISON'S DISEASE: THE EFFECT
OF TREATMENT WITH THE CORTICAL HORMONE OF
THE SUPRARENAL GLAND.**

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THE first positive information regarding the function of the suprarenal glands was obtained with the description of the clinical syndrome now known as Addison's disease. Of recent years there have been many attempts to reproduce this syndrome in animals by extirpation of both suprarenal glands, but the animal (dog or cat) invariably died, usually within 2 weeks. In this respect the experimental picture more nearly corresponds to that seen in cases of suprarenal apoplexy rather than that seen in Addison's disease, which usually runs a subacute or chronic course. In consequence, it was commonly considered that the clinical syndrome of Addison's disease could not be reproduced experimentally in animals. Recent investigators,^{4,37} however, have maintained that many of the phenomena of Addison's disease are similar to those observed in supra-

renalectomized animals. Whereas many symptoms vary in severity in the two conditions, they are qualitatively the same and are to be considered as manifestations of suprarenal insufficiency. Weakness, muscular asthenia, loss of weight, anorexia, gastrointestinal disturbances, and nervous manifestations in particular, are often found both in clinical and experimental conditions.

Extended chemical and metabolic studies have been made of suprarenalectomized animals, and the changes observed have been interpreted in terms of the normal physiologic activity of the suprarenal gland. These studies recently have been reviewed by Britton, and will not be considered in detail here. The clinical features of Addison's disease have been reported in detail by Rowntree and Snell. Thus far, 125 patients with Addison's disease have been observed at The Mayo Clinic. The suprarenal cortical hormone prepared by the method of Swingle and Piffner has, in the last year, been used in the treatment of 20 patients. We shall report here both on the chemical and metabolic changes observed in cases of Addison's disease, and on the effect on these changes of treatment with the suprarenal cortical hormone.

When both suprarenal glands are removed from an animal, whether by means of an operation in one stage or in two stages, suprarenal insufficiency becomes complete with the stroke of the surgeon's knife. The subsequent clinical course is rapidly downward to a fatal termination. The course of the patient with Addison's disease shows many points of similarity, yet the differences are characteristic and fundamental. For the purposes of this consideration the course may arbitrarily be divided into three periods. The distinction between these periods is not always sharp, but they usually are recognizable.

The Three Periods in the Course of Addison's Disease. *The Period of Initial Destruction of the Suprarenal Glands.* Approximately two-thirds of all cases of Addison's disease are due to tuberculosis of the suprarenal glands. One-fifth of the total number are due to atrophy, particularly of the cortex. Experimental studies have disclosed that removal of one suprarenal gland may be compatible with the life of the animal and that bilateral suprarenalectomy is not necessarily fatal if accessory glandular tissue is present. The suprarenal glands in many cases of Addison's disease in which there is a history indicating duration limited to a few weeks, are represented by large caseous or calcareous masses suggestive of a chronic, slowly growing lesion. These observations all suggest that the suprarenal glands possess considerable functional reserve, and that clinically recognizable signs of Addison's disease do not appear until this reserve is seriously impaired or destroyed. When the functional activity of the glands becomes insufficient for the daily physiologic requirements of the body, the second stage is initiated.

The Period of the Recognizable Clinical Syndrome. The characteristic clinical symptoms of Addison's disease, namely, asthenia, pigmentation, loss of weight and strength, and arterial hypotension, are well known. Once they appear the diagnosis is established. Although the efficiency and activity of the patient may be greatly reduced, disability is not necessarily complete. The average length of life following the appearance of the clinical symptoms of Addison's disease is 16.5 months, according to Rowntree, and 13.3 months according to Guttman, although Guttman reported 11 cases in which the duration was more than 5 years. A greater or lesser degree of suprarenal insufficiency must be present during this period, yet the patient is in a fairly satisfactory clinical condition. When we mention the chemical and metabolic changes in Addison's disease, it is to this period that we refer.

The Terminal Period or Crisis. Patients with Addison's disease are exceedingly susceptible to intercurrent infection, and usually are sensitive to fatigue and minor traumas, such as dental extraction. Such predisposing factors frequently initiate an acute, shock-like condition, or a period of crisis, although the latter may also develop spontaneously. This condition is characterized by a severe gastrointestinal upset, nausea and vomiting, pain, circulatory collapse, low blood pressure, cold extremities, and lowered bodily temperature. The urinary output is often reduced and the respiration may have the characteristic irregularity described by Rowntree.

The outcome of such a crisis varies with the severity of the condition. In some cases several such upsets have occurred from which the patients have recovered spontaneously. In other cases, treatment as outlined in the reports of Rowntree, Greene, Swingle and Pfiffner and of Rowntree, Greene, Ball, Swingle and Pfiffner, is strikingly beneficial. Still other patients are refractory to treatment, and the crisis is terminal.

The chemical and metabolic determinations in Addison's disease will be presented on the basis of the last two periods. The change from the one to the other may be insidious, and there is room for difference of opinion so far as the precise severity of symptoms necessary for the establishment of a crisis is concerned, but in general the distinction between the two groups is permissible.

The Basal Metabolic Rate. The respiratory exchange of patients with Addison's disease was first studied by Fuchs and Roth. Löffler, Muirhead, Aub, Forman and Bright, Grafe, Lawrence and Rowe, and Labbé and Stéveninereported cases in which the basal metabolic rate was reduced. Herman and Richard, and Marañon and Carrasco reported other cases in which the metabolic rate was normal or increased. A considerable number of cases was reported by Boothby and Sandiford and by Rowntree. These reports indicate that the basal metabolic rate in this condition, although frequently within

normal limits, is variable, and may be markedly reduced in some cases. We wish to summarize the experience at The Mayo Clinic to date, with the report on the basal metabolic rate in a series of 86 cases of Addison's disease. A preliminary study indicated that the basal metabolic rate, when calculated according to the Aub-DuBois standard in the usual way, fell, for the most part, within the lower limits of normal. Experience at the Clinic, however, has indicated that the mean basal metabolic rate of normal persons varies, depending on the age group studied. In younger persons it may be from -3 to -7 per cent. Under these conditions it becomes

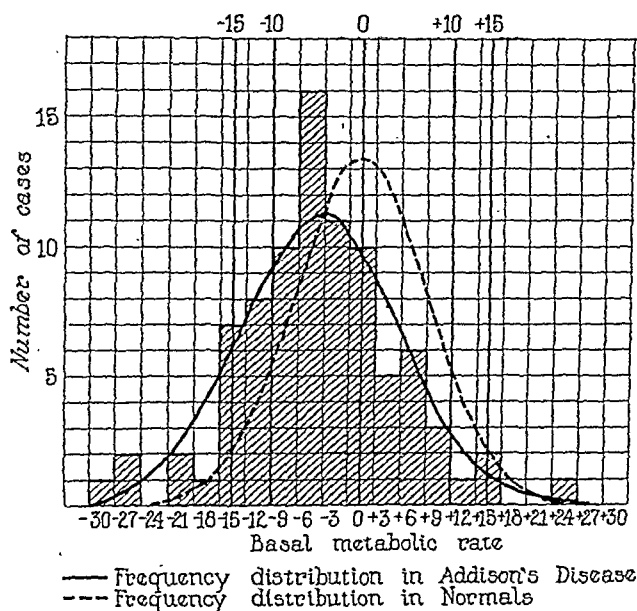


FIG. 1.—The frequency of distribution of basal metabolic rates in a series of 86 patients with Addison's disease. The calculated distribution curve is shown: mean, -4.8 ± 0.67 ; standard deviation, 9.2 ± 0.48 . The distribution curve for normal men aged 40 to 44 years is given for comparison: mean, 0.0 ± 0.34 ; standard deviation, 7.7 ± 0.24 .

difficult to judge of the statistical validity of the apparent reduction of the basal metabolic rate observed in cases of Addison's disease. To facilitate comparison the latter rates were recalculated according to the new standards of Boothby and Sandiford. The frequency distribution is shown in Fig. 1, together with the distribution curve found by Boothby and Sandiford for normal men aged 40 to 44 years.

The basal metabolic rate unquestionably is reduced in Addison's disease, with a mean value of approximately -5 per cent and a mode of approximately -7 per cent. Very low values are found in certain cases, and there is a suggestion that these low values are more

frequently found in crisis. The condition of the patient in crisis, however, precludes any very extended study of respiratory exchange at that time.

It is generally recognized that the basal metabolic rate is reduced to the extent named, or more, in conditions characterized by undernutrition. Loss of weight and muscular asthenia are cardinal symptoms in Addison's disease, and the reduction in respiratory exchange in consequence may be a secondary phenomenon, although we have not found direct correlation between the loss in weight and the basal metabolic rate.

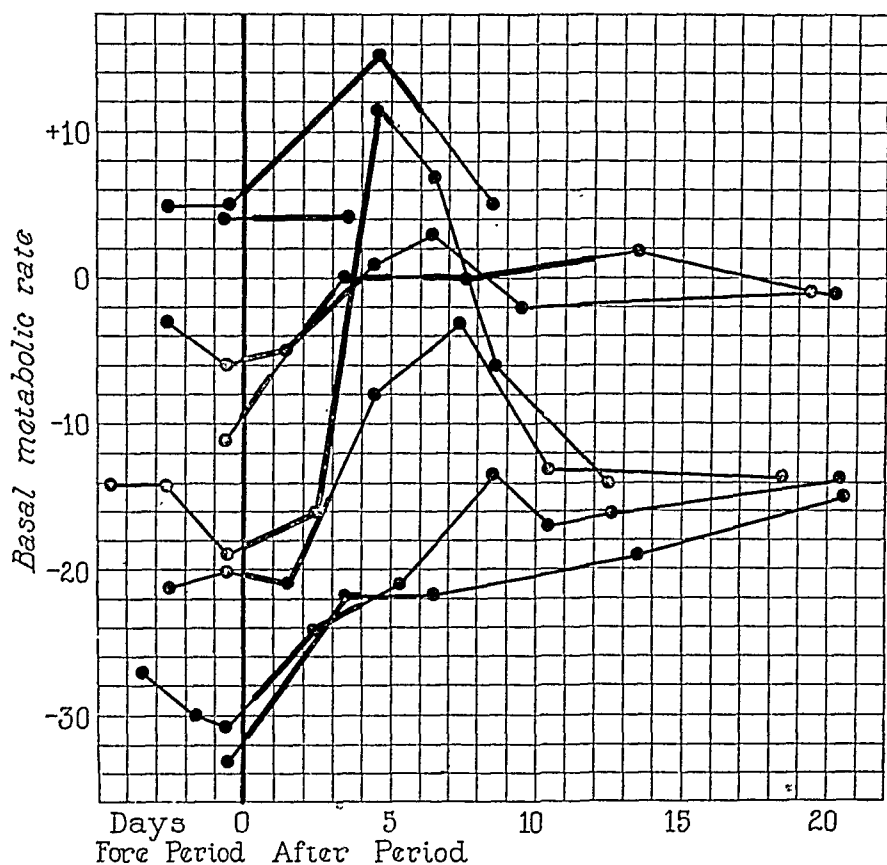


FIG. 2.—Changes in the basal metabolic rate of patients with Addison's disease treated with the suprarenal cortical hormone. The days on which treatment was given are marked by the heavy line.

Investigators who have determined the respiratory exchange in animals after suprarenalectomy have considered the changes to be direct results of the suprarenal insufficiency. The earlier studies were discordant, but Aub, Forman and Bright, Houssay and Artundo, Swingle, Pfiffner and Webster, and Harrop, Pfiffner, Weinstein and Swingle all have reported reduction in the basal metabolic rate. The last-named investigators found that the basal

metabolic rate of animals which had reached the stage of prostration was approximately 50 per cent below normal. Forty-eight to 72 hours after administration of the cortical hormone the metabolic rate rose to between 10 and 18 per cent above the normal previously established for an individual animal.

The effect of treatment with the cortical hormone on the metabolism of patients with Addison's disease (Fig. 2) is variable. There is very little change in patients whose metabolic rate is normal. When the metabolic rate of the patient is reduced, treatment causes elevation toward, although not always to within, normal limits: thus in Case 12 the change was from -31 to -13 per cent and in Case 16 from -22 to -4 per cent. The maximal increase was from -18 to $+12$ per cent, and in no case did the basal metabolic rate after treatment rise above $+14$ per cent. The increase in the basal metabolic rates of these patients may in part be associated with the increased strength and vitality of the patient, but this is not necessarily the case, for we have observed marked clinical improvement associated with considerable gain in weight without any corresponding change in the metabolic rate.

That the change in the respiratory exchange is not an accurate guide to the clinical condition is also indicated by 3 cases in which there were considerable increases in metabolic rate, with only a questionable degree of clinical improvement.

The study of the respiratory exchange of this group of patients shows that the clinical features are in harmony with experimental results in indicating some degree of reduction in the basal metabolic rate in the presence of suprarenal insufficiency, and in demonstrating improvement following treatment with cortical extract. The results with patients, however, are much less marked than are those with animals, and do not serve to determine whether these changes are direct results of the suprarenal insufficiency or whether they are secondary to the associated nutritional disturbance.

Nitrogen Metabolism. The earliest studies of the composition of the urine and of the nitrogen balance in Addison's disease, as pointed out by Grafe, may be discounted because of the inadequacy of the analytic methods then available, even though the results were not significantly different from normal. The more recent investigations, such as those of Kolisch and Pichler, Senator, Vollbracht, Pickardt, Wolf and Thacker, Eiselt, and Beuttenmüller and Stoltzenberg, are free from this objection.

We have studied the partition of urinary nitrogen and the approximate nitrogen balance in 9 cases of Addison's disease, before, during, and after treatment with the suprarenal cortical hormone. Because of the anorexia and gastrointestinal distress that accompanies many cases of untreated Addison's disease, it has not been possible to put these patients on a constant, rigid diet. It has been necessary, instead, to allow the patient to eat as desired, but all food served

and any uneaten portion was weighed. In this way a record was kept of all food actually consumed. The content of nitrogen and calories was then calculated from the Atwater-Bryant tables. The stools were not saved, but in calculating the nitrogen balance, the fecal nitrogen was assumed to be one-tenth of the intake. Care was taken in the collection of urine, and the periods over which the daily specimens of urine were collected were, for the most part, accurate to within 15 minutes. The analytic methods of Folin were used throughout in urinalysis.

The analytic results in illustrative cases are given in Tables 1, 2, 3, 4, 5 and 6. The details of the clinical histories have been given in the paper of Rowntree, Greene, Ball, Swingle and Pfiffner. For the most part, the composition of the urine corresponded to the lower level of the usually accepted normal standards. The total nitrogen varied between 5.30 and 11.77 gm. for 24 hours. Urea was the major constituent. The values for the creatinin nitrogen, uric acid nitrogen, amino-acid nitrogen and rest nitrogen all fell within the limits of normal, and to this extent served to exclude disturbances in endogenous metabolism. There was no change in these values with treatment. The acid-base balance, as indicated by the hydrogen-ion concentration, the titratable acidity, the ammonia nitrogen or the excretion of phosphate was likewise normal, and was not significantly changed during treatment.

We have found a considerable degree of creatinuria (more than 30 mg. of creatin nitrogen daily, or more than 10 per cent of the preformed creatinin) in 7 of 13 cases studied. When creatin has been present it has been reduced in amount or has disappeared completely as a result of treatment with the cortical hormone (Table 1). Especial mention should be made of the excretion of urea in the ninth case in our experience (Table 3) which, as has been said, is reported in another paper. This patient was weak, but was in a satisfactory clinical condition on the first day of the metabolic study. The second day he had no appetite, ate very little, vomited once, and took only a small amount of fluid; the amount of urine was greatly reduced. Treatment with cortical hormone was started, the intake of fluid was pushed during the next two days, and the patient made a prompt and spectacular clinical recovery. The elimination of practically all urinary constituents was reduced the day the urinary output was diminished. That this was due to retention is shown by the increased excretion the 2 following days. This is well shown by the figures for urea, creatinin and titratable acidity. The output of total nitrogen the second day of the experiment was 5.83 gm. less than on the first day. Approximately this amount of extra nitrogen was eliminated in the next 2 days. The intake of food was reduced during this period. This effect, plus the washing out of retained nitrogen, resulted temporarily in a very markedly negative nitrogen balance.

TABLE 2.—THE EFFECT ON METABOLISM OF TREATMENT WITH CORTICAL HORMONE IN THE EIGHTH CASE OF OUR EXPERIENCE.

	December.					January.										
	27	28	29	30	31	1	2	3	4	5	6	7	8	9	10	11
Weight, kg.	62.10	...	61.80	...	61.70	...	62.10	62.10	...	63.90	...	63.00	...	63.00	...	62.80
Cortical hormone, cc.	10	10	10	15	15
Intake of food:
Total calories	1750	2100	2700	2650	2850	2500	2750	2950	2300	2675	2400	2700	2600	2750	2400	2300
Protein expressed as nitrogen, gm.	8.00	8.80	10.40	10.40	11.20	10.40	11.20	11.20	9.60	8.80	9.60	10.40	9.60	9.60	10.40	11.20
Basal metabolic rate, per cent	-14	...	-14	...	-19	-16	...	+12	...	+7	...	-6	...	-12
Urine for 24 hours:
Volume, cc.	1600	...	1750	1610	1300	1400	1410	1850	1150	1150	...	1400	1230	1210	1420	1510
Total nitrogen, gm.	11.77	...	10.75	9.98	8.12	8.93	8.37	9.60	7.51	7.93	...	9.90	7.93	7.72	9.16	9.96
Urea nitrogen, gm.	9.73	...	9.04	8.37	6.85	7.36	7.42	8.35	6.16	6.47	...	7.73	6.61	6.57	7.84	8.63
Ammonia nitrogen, gm.	0.37	...	0.15	0.14	0.09	0.37	0.14	0.22	0.20	0.42	...	0.37	0.19	0.19	0.25	0.29
Total creatinin nitrogen, gm.	0.69	...	0.59	0.53	0.46	0.59	0.56	0.58	0.47	0.50	...	0.59	0.46	0.44	0.52	0.56
Prot. creatinin nitrogen, gm.	0.66	...	0.59	0.48	0.44	0.57	0.52	0.56	0.47	0.49	...	0.57	0.44	0.43	0.48	0.53
Creatin nitrogen, gm.	0.03	...	0.05	0.05	0.02	0.02	0.04	0.07	0.02	0.01	...	0.02	0.02	0.01	0.01	0.03
Amino nitrogen, gm.	0.09	...	0.06	0.06	0.09	0.06	0.07	0.07	0.05	0.06	...	0.07	0.06	0.05	0.05	0.06
Uric acid nitrogen, gm.	0.16	...	0.15	0.14	0.12	0.12	0.15	0.17	0.15	0.15	...	0.19	0.16	0.14	0.16	0.17
Rest nitrogen, gm.	0.83	...	0.76	0.74	0.51	0.43	0.52	0.21	0.46	0.33	...	0.95	0.45	0.33	0.34	0.25
Nitrogen balance, gm.	-4.57	...	-1.39	0.62	+1.96	+0.43	+1.21	+0.48	+1.13	-0.01	...	-0.54	+0.71	+0.92	+0.20	+0.12
Total acids, cc. N/40	317	...	223	239	110	365	340	508	178	121	...	305	142	243	305	247
Phosphate, gm.	0.97	...	0.93	0.75	0.49	0.60	0.86	0.87	0.65	0.74	...	0.81	0.66	0.89	1.12	0.82
Sodium chlorid, gm.	13.12	...	15.03	11.52	9.38	12.48	10.80	14.43	10.51	9.50	...	14.28	10.41	9.94	8.29	14.50
Blood:
Urea, mg. in each 100 cc.	28	30	32	...
Sulphates, mg. in each 100 cc.	6.4	3.5	...

TABLE 3.—THE EFFECT ON METABOLISM OF TREATMENT WITH CORTICAL HORMONE IN THE NINTH CASE OF OUR EXPERIENCE.

	January.												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Weight, kg.	54.00	15	15	54.40	15	51.70	55.10	56.00	55.50	55.50
Cortical hormone, cc.	15
Intake of food:													
Total calories	2500	900	700	1500	1250	1050	2650	2400	2650	2850	2450	2600	2700
Protein expressed as nitrogen, gm.	10.40	1.60	5.60	9.60	7.20	10.40	11.20	11.20	11.20	11.20	10.40	12.00	9.60
Basal metabolic rate, per cent	+1	-7	...	+1	...	-5	-9	...
Urine for 24 hours:													
Volume, cc.	1400	780	1800	1520	1050	950	1250	1100	1440	...	1300	1410	1230
Total nitrogen, gm.	10.56	4.73	12.24	13.52	10.25	9.65	9.98	8.44	9.51	...	7.73	7.54	7.65
Urea nitrogen, gm.	8.85	3.67	10.36	11.53	8.63	7.65	8.25	7.41	8.43	...	6.65	6.33	6.69
Ammonia nitrogen, gm.	0.21	0.19	0.34	0.39	0.31	0.47	0.33	0.23	0.17	...	0.20	0.13	0.14
Total creatinin nitrogen, gm.	0.59	0.41	0.65	0.56	0.39	0.57	0.47	0.36	0.44	...	0.38	0.44	0.41
Preformed creatinin nitrogen, gm.	0.57	0.39	0.63	0.52	0.37	0.54	0.44	0.35	0.44	...	0.38	0.42	0.39
Creatin nitrogen, gm.	0.02	0.02	0.02	0.04	0.02	0.03	0.03	0.01	0.05	...	0.04	0.02	0.02
Amino nitrogen, gm.	0.05	0.04	0.07	0.05	0.04	0.06	0.05	0.05	0.05	...	0.13	0.05	0.05
Uric acid nitrogen, gm.	0.11	0.06	0.19	0.21	0.16	...	0.13	0.12	0.16	...	0.13	0.11	0.11
Rest nitrogen, gm.	0.75	0.36	0.63	0.78	0.72	0.83	0.75	0.27	0.28	...	0.33	0.48	0.26
Nitrogen balance, gm.	-1.20	-3.29	-7.20	-5.88	-3.75	-0.29	+0.10	+1.64	+0.57	+	+1.63	+3.26	+0.99
Total acids, cc. N/10.	217	83	361	374	230	294	227	178	157	...	236	324	270
Phosphate, gm.	0.58	0.20	0.74	0.86	0.49	0.54	0.50	0.39	0.50	...	0.51	0.50	0.53
Sodium chlorid, gm.	6.66	2.15	7.81	9.48	6.30	4.95	7.73	9.11	12.73	...	10.62	9.72	9.70
Blood:													
Urea, mg. in each 100 cc.	66	...	56	...	46	28
Sulphates, mg. in each 100 cc.	7.73	7.95	4.15

TABLE 5.—THE EFFECT ON METABOLISM OF TREATMENT WITH CORTICAL HORMONE IN THE TWELFTH CASE OF OUR EXPERIENCE.

	February.											
	8	9	10	11	12	13	14	15	16	17	18	19
Weight, kg.	49.30	49.70	49.70	49.90	49.80	50.20	50.80	51.50	51.90	51.70	51.70	51.70
Cortical extract, cc.	15	15	15	15
Intake of food:												
Total calories	1625	1600	1760	1835	2385	2400	2360	2350	2450	2000	2450	2740
Protein expressed as nitrogen, gm.	7.20	7.20	8.00	8.00	11.20	11.20	11.20	10.40	11.20	11.20	11.20	11.20
Basal metabolic rate, per cent	-27	-30	-31	-24	-21	-13
Urine for 24 hours:												
Volume, cc.	1000	1310	1850	1690	1780	1590	1700	1790	1850	1510	1260	1280
Total nitrogen, gm.	8.20	9.47	8.50	8.17	8.52	6.21	6.85	7.11	5.71	6.99	7.09	7.19
Urea nitrogen, gm.	6.85	7.79	6.02	6.58	7.07	5.24	5.79	5.94	4.84	5.98	5.74	6.03
Ammonia nitrogen, gm.	0.54	0.72	0.54	0.60	0.46	0.35	0.35	0.31	0.19	0.31	0.32	0.29
Total creatinin nitrogen, gm.	0.39	0.51	0.40	0.43	0.46	0.32	0.35	0.41	0.29	0.39	0.40	0.37
Preformed creatinin nitrogen, gm.	0.38	0.49	0.38	0.43	0.43	0.31	0.31	0.40	0.01	0.02	0.01	0.01
Creatin nitrogen, gm.	0.01	0.02	0.02	...	0.03	0.01	0.01	0.01	0.01	0.02	0.01	0.01
Uric acid nitrogen, gm.	0.14	0.17	0.16	0.16	0.18	0.14	0.14	0.15	0.12	0.15	0.15	0.17
Rest nitrogen, gm.	0.28	0.32	0.48	0.40	0.35	0.15	0.23	0.30	0.26	0.39	0.48	0.33
Nitrogen balance, gm.	-1.72	-1.99	-1.30	-0.97	+1.56	+3.87	+3.53	+2.25	+4.37	+3.09	+2.90	+2.89
Total acids, cc. N/10	259	335	335	258	324	356	365	280	468	290	423	349
Phosphate, gm.	0.47	0.47	0.44	0.42	0.34	0.29	0.31	0.32	0.26	0.37	0.45	0.42
Sodium chlorid, gm.	7.16	8.91	8.80	7.16	8.58	7.22	8.29	10.49	9.26	9.05	10.36	10.48
Blood:												
Urea, mg. in each 100 cc.	56	22	...	26
Sulphates, mg. in each 100 cc.	6.64	4.34	...	3.52

The effect of treatment with the cortical hormone in increasing appetite and causing gain in weight has been stressed by Rowntree, Greene, Ball, Swingle and Pffner. This is well shown in the figures for intake of food in Tables 3, 5 and 6. The initial nitrogen balance in this group of patients apparently varied with the status of the weight curve at the onset of the experiment; it was positive in the 2 cases in which the patients were gaining weight and was in equilibrium or negative in the cases in which the weight was constant or falling. The majority of patients gain weight as a result of this form of treatment. This is accompanied by retention of nitrogen with a corresponding shift in the nitrogen balance. In the 14th case in our experience (Table 6) there was a maximal daily retention of 10.09 gm. of nitrogen. A normal concentration of blood urea at that time indicated that this positive balance was evidence of growth and not of urinary retention. At no time was there evidence of an abnormal or toxic destruction of protein.

Renal Function. Numerous observers since the time of Marshall and Davis have called attention to the increase in blood urea and the evidence of renal insufficiency in suprarenalectomized animals. By some this has been considered to be one of the earliest signs of suprarenal insufficiency.

It is recognized that renal insufficiency may be manifest during the critical periods and terminal stages of Addison's disease. It has been our clinical experience that an adequate intake of fluid is necessary in these cases, and that reduction in the latter, sufficient to permit a urinary output of less than 1 liter a day for 2 or 3 days, may be of serious consequence. We have reported evidence of retention of urea in particular during such an episode.

Study of patients with Addison's disease who were in good clinical condition and whose intake of fluid was adequate, for the most part reveals normal values for blood urea and for excretion of phenolsulphonaphthalein. The values for urea in each 100 cc. of blood were practically all less than 40 mg. (Fig. 3). Values of more than 50 mg. with a maximal value of 154 mg. were found only if patients were in crisis, vomiting, dehydrated, or who were in collapse or were recovering from this condition. An intensive study of renal function of a patient in crisis is not practicable, and our observations were limited. There is a suggestion, however, that the excretion of phenolsulphonaphthalein is reduced at such times. The concentration of creatinin in the blood may be increased when the patient is in crisis; the maximal value observed was 4.8 mg. in each 100 cc. The blood creatinin is a less sensitive index in these cases than is the blood urea and may still be within the normal limits when the latter is considerably elevated. The decrease in the values for blood urea and creatinin in such a case following treatment with the cortical hormone and the supplying of an adequate amount of fluids is shown in Fig. 4. The concentration of uric acid in the

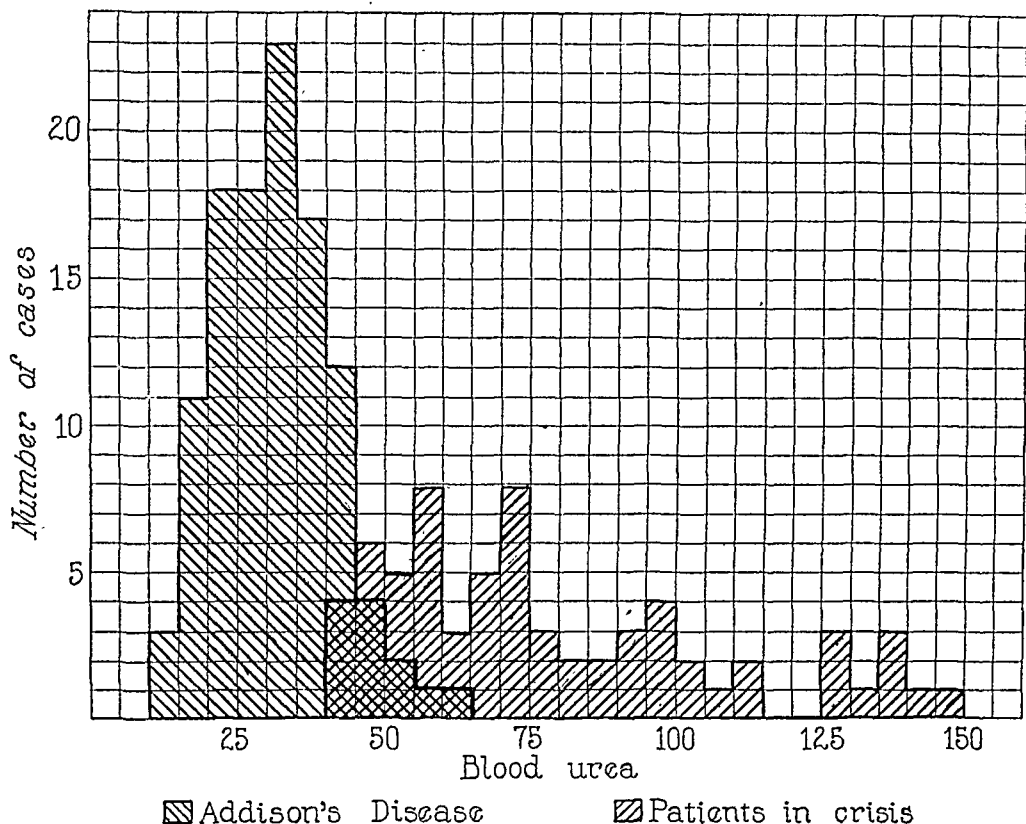


FIG. 3.—The frequency of distribution of the concentration of urea in the blood in a series of cases of Addison's disease. Cases in which the concentration of urea was 40 mg. in each 100 cc. of blood, or more, and in which the patient was in crisis or was recovering from crisis, are marked.

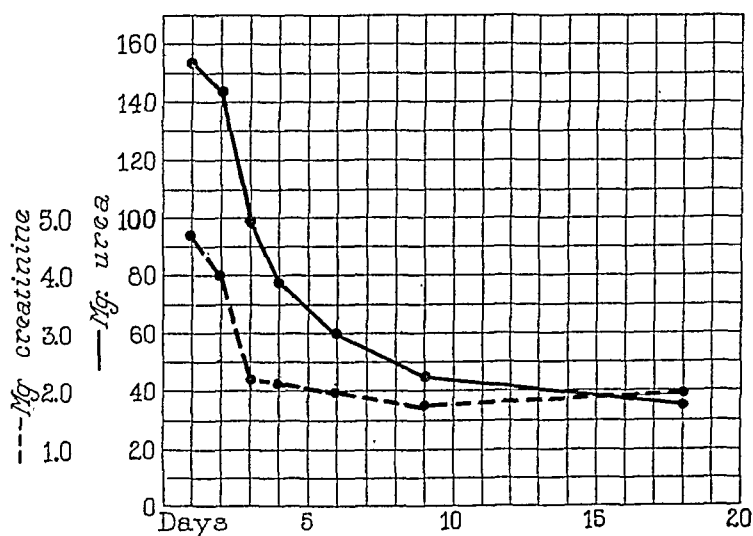


FIG. 4.—The change in the concentration of blood urea and of creatinin, in consequence of treatment of a patient with Addison's disease who was in crisis. Ten cubic centimeters of the suprarenal cortical hormone were given daily during the first week, and the daily intake of fluid was 2000 cc. or more during the period of observation.

blood has been recommended as an index of renal insufficiency, but it did not depart from normal in this group of patients. Wakefield has pointed out the significance of an increase in the sulphates of the serum as an early sign of renal insufficiency. In Addison's disease he found the concentration of sulphates to be normal except during the critical periods and terminal stages of the disease. We are able to confirm this observation. The maximal value obtained was 13.5 mg. in each 100 cc. Occasionally, the value for sulphates in the serum is slightly increased in a case in which the value for blood urea is normal and in which the patient is in fairly good clinical condition. This may well be an incidental observation, for it has been our experience that although there is retention of urea, creatinin and sulphates in the blood of a patient in crisis, and that a period of increased intake of fluid, with diuresis, will dispel this retention, the sulphates are the last to be eliminated and the slowest to return to normal. We have also observed 1 patient who died from Addison's disease, whose blood urea and sulphates were kept within a normal range by means of forced administration of fluids. These results we believe indicate that renal insufficiency in Addison's disease is a secondary manifestation, dependent primarily on such factors as dehydration and circulatory collapse rather than being a direct manifestation of suprarenal insufficiency.

Other elements may enter into this response. Rowntree and Rosenow have both called attention to the delay in the excretion of water by these patients, and a change in the water balance may predispose to anhydremia. However, the fundamental relations we believe are those outlined.

Carbohydrate Metabolism. *Blood Sugar.* There has been much discussion of the relationship between the suprarenal glands and the metabolism of carbohydrates. Most of this discussion has been concerned primarily with the part played by epinephrin in physiologic processes. Porges was the first to report decreased values for blood sugar in Addison's disease. The early reports were contradictory. They have been summarized by Rosenow and Jaguttes, who pointed out that hypoglycemia was a frequent but not a constant occurrence. More recent reports have been those of Lawrence and Rowe, Rowntree and Snell, and Chapman.

A study of patients with Addison's disease disclosed that the fasting blood sugar, determined by the Folin-Wu method, varies between 70 and 130 mg. in each 100 cc. with the value in the majority of the cases between 70 and 105 mg., and the peak of the distribution curve between 85 and 90 mg. Values below 70 mg. were found only if patients were in crisis, and we have seen 12 cases in which the readings of blood sugar were between 45 and 70 mg. This degree of hypoglycemia does not necessarily accompany the state of crisis, and normal values for blood sugar may be present at the time of crisis. We agree with Wadi in considering that

hypoglycemia is essentially a phenomenon of collapse. Symptoms suggestive of this condition have been observed by us, but are much confused with the preëxisting evidences of circulatory failure, coma and collapse. In such cases, gradual increase in the fasting blood sugar has been associated with recovery following treatment.

The slight reduction in the fasting blood sugar seen in cases of Addison's disease may be an expression of the anorexia and poor nutritional state which is characteristic of this disease. If, as suggested by others, it represents a characteristic and fundamental disturbance in carbohydrate metabolism, this must be of a special type unrelated to that seen in diabetes mellitus, for we have seen 2 cases, reported by Allan, in which the two diseases were coëxistent.

Lactic Acid. The metabolism of lactic acid is closely related to that of carbohydrates. The lactic acid content of the blood of 4 patients with Addison's disease varied between 5.1 and 11.3 mg. in each 100 cc. These are within the usual normal limits, although they come within the lower portion of the latter. Hastings and Compere reported a decrease in the lactic acid content of the blood of suprarenalectomized dogs, although this observation was not confirmed by the studies of Harrop, Pfiffner, Weinstein and Swingle.

Further Study of the Chemical Condition of the Blood. Some of the changes in the chemical composition of the blood in Addison's disease have been considered previously (Table 7). Various other changes have been reported in animals following suprarenalectomy. The values for total solids, protein, calcium and potassium are increased, and those for chlorids are decreased. Uncompensated acidosis, with changes in hydrogen-ion concentration, carbon dioxid tension, and carbon dioxid combining power also have been reported. We can confirm the presence of similar changes in clinical cases but again find that the severity of the disturbance varies with the stage of the disease (Table 5). The concentration of serum proteins varies from 5.0 to 7.9 mg. in each 100 cc. among patients who are in good condition. Values between 8.3 and 9.9 mg. were found at the time of crisis. The values for calcium were normal in the cases of the first group, but they varied between 11.6 and 13.5 mg. in each 100 cc. of blood in the cases in crisis. The values for potassium were similarly changed, but these changes were not as striking as those reported in dogs by Hastings and Compere. These observers reported increases much greater than could be explained by the concentration of the blood. The changes in the serum protein and calcium observed in cases of Addison's disease are characteristic of dehydration, or anhydremia, with concentration of the blood. Direct evidence of anhydremia during crisis has also been presented by Rowntree and Brown, who found the blood volume and plasma volume reduced at such times, although normal values were the rule when the patient was in good condition. Changes in the blood which are consequent on dehydration and concentration

TABLE 7.—THE CHEMICAL COMPOSITION OF THE BLOOD OF PATIENTS WITH ADDISON'S DISEASE.

Serum protein, mg. in each 100 cc.	Serum calcium, mg. in each 100 cc.		Serum potassium, mg. in each 100 cc.		Serum inorganic sulphate, mg. in each 100 cc.		Serum chlorids, mg. in each 100 cc.		Carbon dioxide com- bining power, cc. in each 100 cc. plasma.		Lactic acid, mg. in each 100 cc.	Blood sugar, mg. in each 100 cc.
	In chron- icity.	In crisis.	In chron- icity.	In crisis.	In chron- icity.	In crisis.*	In chron- icity.*	In crisis.*	In chron- icity.*	In crisis.*		
6.3	10.8	11.8	16.3	25.2	4.9	6.7	645	565	52	40	9.0	70
7.3	10.4	11.8	19.3	28.8	3.5	6.4	575	540	48	30	11.3	90
7.9	10.8	11.6	17.8	33.3	3.2	6.6	605	445	60	48	5.9	105
5.7	8.3	12.4	17.9	...	3.3	7.7	579	540	58	44	5.1	50
5.0	10.5	13.5	24.2	...	4.3	8.0	620	569	48	47	11.7	50
7.1	9.4	...	20.1	...	3.5	10.5	578	300	45	54	14.2	45
...	10.0	...	24.0	...	3.2	13.3	694	495	55	56	...	43
6.8	4.1	7.8	651	535	52	35	...	58
						10.1	594	528	41	46	...	67
						11.7	519	536	68	36	...	85

* Ten cases taken at random; complete data not given.

must be considered secondary and not direct results of suprarenal insufficiency.

The values for serum chlorids may be low in Addison's disease, although not markedly so, for we find a variation of between 519 and 711 mg. in each 100 cc. Certainly the values are not greatly different from the usually accepted figures for the normal. Lower values occur when the patient is in crisis, 445 to 569 mg. Anorexia and vomiting are both pronounced at the latter time, and the combined effects of reduced intake of salt and loss of chlorids in the gastric content may well account for this reduction. We have previously pointed out that urinalysis did not indicate any great disturbance of the acid-base balance of patients with Addison's disease. The carbon-dioxid combining power of the blood has varied between 41 and 68 volumes per cent of plasma in such cases. Some, but not all, patients who were in crisis gave evidence of acidosis. The range of variation of the carbon dioxid combining power in this group was between 30 and 50 by volumes per cent. The retention of sulphates and of acids in consequence of renal insufficiency has been considered, and such retention may be a factor in producing acidosis. We have recently seen a patient in the terminal stages of Addison's disease to whom it was possible to administer sufficient fluids to insure adequate renal function and to maintain the blood urea and sulphates at normal levels. She was unable to take food, and after several days of virtual starvation the carbon dioxid combining power fell to 15 volumes per cent, while large amounts of acetone and diacetic acid appeared in the urine. Considerable reduction in the degree of acidosis occurred in consequence of intravenous administration of glucose. The acidosis of this patient was due primarily to the ketosis of starvation. These results correspond in great part to those reported by Marañón. They suggest that although patients with Addison's disease as well as suprarenalectomized dogs show disturbances in the acid-base equilibrium, these changes apparently are secondary and are not to be considered as primary manifestations of suprarenal insufficiency. Cholesterol and the blood lipoids were also studied in a few cases, but the results were not greatly changed from normal.

Acidity of Gastric Content. Although gastrointestinal disturbances and epigastric pain, suggestive of hyperacidity, are common in Addison's disease, hyperacidity is only occasionally demonstrable by analysis of gastric content. Achlorhydria was present in approximately half of the cases studied, and subacidity in another fourth of them. Analysis of gastric content has not been done as a routine on patients under treatment. There is no change in some cases. On the other hand, one patient with complete achlorhydria to the ordinary Ewald test meal was found to have a free acid of 34 and a total acidity of 50 (in terms of cubic centimeters of 0.1 normal sodium hydroxid) after completion of a course of treatment with cortical hormone.

Comment. These results demonstrate the many points of similarity between the chemical and metabolic changes observed in cases of Addison's disease and those reported in suprarenalectomized animals. They also reveal that in the study of these changes the clinical condition of the patient must be considered carefully to exclude the influence of secondary effects not solely ascribable to suprarenal insufficiency.

The patients with Addison's disease in the group studied who were suffering from muscular weakness and asthenia, pigmentation of the skin, anorexia, and loss of weight, but who were otherwise in good clinical condition and were not vomiting or were not dehydrated, had few metabolic abnormalities. The basal metabolic rate usually was slightly reduced. Gastric achlorhydria was common, creatinuria was sometimes present, and the level of fasting blood sugar was slightly reduced. If the patient was losing weight the nitrogen balance was negative. These changes may in part be an expression of the poor nutritive condition of the patient as well as an expression of suprarenal insufficiency.

During a period of crisis, with vomiting, dehydration and circulatory collapse, the effects of anhydremia and renal insufficiency dominate the metabolic picture. The blood volume is reduced; the values for serum protein, calcium and potassium are increased. There is retention of urea, creatinin, sulphates and acid products in the serum; this last may result in a moderate degree of acidosis, although ketosis from starvation may also be a factor in the production of acidosis. Hypoglycemia may be a terminal event. The effects of anhydremia and renal insufficiency may be prevented or eliminated by the administration of adequate amounts of fluid, without preventing a fatal termination of the disease. Usually provision of an adequate supply of fluids has a favorable influence on the clinical course of the disease.

The therapeutic use of the cortical hormone, as we have pointed out, reduces nausea and allays vomiting in the crisis of Addison's disease, and therefore greatly facilitates the administration of adequate amounts of fluids. Under these conditions the evidences of anhydremia and renal insufficiency disappear rapidly. With continued improvement patients gain in weight, the nitrogen balance becomes positive, creatinuria disappears, and the metabolic rate often returns to normal, although this last may be in part only an expression of the improvement in the general state of nutrition.

The paucity, in Addison's disease, of chemical and metabolic changes which can be ascribed solely to suprarenal insufficiency, is significant. Experience with the preparation for therapeutic use of other hormones, such as insulin, pituitary extract, or the parathyroid hormone, which cannot as yet be identified by precise chemical means, has emphasized the importance of rapid and accurate methods of standardizing the activity of commercial preparations. The ability of the cortical hormone indefinitely to

prolong the life of bilaterally suprarenalectomized cats was the measure of its efficiency originally used by Swingle and Pfiffner. Other biochemical methods of standardizing this or similar preparations have since been suggested as being simpler and more rapid, but their validity remains to be demonstrated.

Summary. A study has been made of the chemical and metabolic changes observed in cases of Addison's disease, and the effect on these changes of treatment with the cortical hormone of the suprarenal gland.

It is emphasized that the clinical course of a case of Addison's disease may arbitrarily be divided into three stages: (1) The stage of initial destruction of the suprarenal glands; (2) the stage of the recognizable clinical syndrome, and (3) the terminal stage or crisis.

Usually the disease is not recognized until the second stage is reached. At this time there may be loss of weight, asthenia and definite undernutrition. The basal metabolic rate is reduced slightly and there is some reduction in the blood sugar. Such changes become less with treatment, and more marked in the periods of crisis.

The quantities of the various constituents of the urine in Addison's disease corresponded to the lower levels of the usually accepted normal standards. Creatinuria was present in a considerable proportion of cases. Retention of practically all urinary constituents was noted in one case in the course of a period of diminished urinary output. The nitrogen balance of those patients who were losing weight was negative. The majority of patients gained weight as a result of treatment with the suprarenal cortical hormone. In such cases the nitrogen balance became markedly positive.

The period of crisis was characterized by gastrointestinal upsets, nausea and vomiting, pains, circulatory collapse, low blood pressure, dehydration and renal insufficiency. The effect of the last two dominated the chemical picture at this time.

The relation between the chemical and metabolic changes observed in cases of Addison's disease, and those reported in suprarenalectomized animals, and the use of these changes for the standardization of preparations of the suprarenal cortical hormone are considered.

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ENTERAL ADMINISTRATION OF INSULIN TO NORMAL DOGS.*

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CONSIDERABLE data have been published that deal with the absorption of insulin by the alimentary tract. Stammers' review of the records, however, shows that insulin administered in this way is ineffective. Usually the failure of oral or enteral administration of insulin has been attributed to its destruction by pepsin or trypsin, and numerous attempts have been made to inhibit the action of these enzymes. Murlin, Sutter, Allen and Piper found evidence of the utilization of sugar in cases of diabetes after insulin in crude solution containing 0.1 per cent hydrochloric acid, had been instilled directly into the duodenum. They also found that insulin in enteric-coated tablets sometimes passed through the stomach and survived the action of trypsin long enough to produce improvement of the diabetes. Peskind, Rogoff and Stewart found that insulin in serum, defibrinated blood, or water was absorbed from the rectum of rabbits, but relatively large doses were necessary, and the effect on blood sugar was more transitory than when smaller doses were given subcutaneously. Administration of insulin by rectum in a solution of sodium chlorid, water or serum, did not affect normal or depancreatized dogs.

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Gaebler and Murlin, working with dogs with phlorhizin diabetes, observed that insulin administered orally, in enteric-coated tablets, combined with malic acid, sodium oleate, and an amino-acid which liberated hydrochloric acid, also administered in solution in blood serum, caused positive, although moderate, reduction of sugar in the urine and increase in the respiratory quotient, and spared protein. The effect was much less than that produced by subcutaneous administration. Similar results with depancreatized dogs were obtained by Murlin and Hawley, who proved that if insulin were protected by blood serum from proteolytic destruction by digestive enzymes, it could be absorbed in significant amounts by the alimentary tract. In some instances the respiratory quotient was raised as high as the value following subcutaneous injection. In several instances the urine was entirely freed of sugar, although the dog was taking a full diet containing meat. The effect on the blood sugar was not as sudden or as great as when insulin is given subcutaneously. The liver seemed to protect the body against the severe effects of a sudden access of insulin to the general circulation. Hypoglycemic symptoms have never been observed following enteral administration of insulin even in huge doses. Four of Murlin and Hawley's dogs were kept alive 81, 125, 41 and 91 days, respectively, after complete pancreatectomy, and while they were on full diets.

Most of the effects of oral or enteral administration of insulin to normal animals have been entirely negative.^{1,11} Administration of insulin by rectum to rabbits fails, according to Senstrom, because it is inactivated by the feces. Supniewski, Ishkawa and Geiling have expressed the belief that the large size of the insulin molecule prevents its passage into the circulation when it is injected into the cerebellar cistern. Subcutaneous injections of insulin produced marked decreases in the sugar of the blood and spinal fluid of dogs and rabbits, but intraspinal injection was without effect.

We have used dogs with permanent fistulas at different levels of the gastrointestinal tract so that solutions could be instilled directly or material withdrawn at the desired level. It would appear that direct instillation should avoid the possibility of destruction by enzymes at other intestinal levels. The results were all uniformly negative; as far as could be demonstrated there was not any marked effect on the concentration of sugar in the blood. Control experiments demonstrated that small amounts of insulin absorbed in the portal circulation produced definite decrease in the sugar of the blood. Since these experiments seemed to indicate that effective amounts of insulin did not pass through the normal intestinal mucosa we believed that they might be of some interest.

Experimental Procedures. The intestinal fistulas were made by a method of Mann and Bollman which permits ready and frequent passage of a small catheter through a small, exposed segment of intestine, directly into the portion of intestine to which this segment

is anastomosed. Large amounts of solutions thus can be injected directly into the intestine, and in our experiments there was no leakage of injected material. Other animals were prepared so that there were isolated intestinal loops. The loop isolated was about 30 cm. of ileum taken about 75 cm. from the distal end of the ileum and the upper and lower ends were left in the upper and lower ends of the abdominal wound to drain externally. The insulin used was Iletin (insulin-Lilly) U20 or U80 of tested potency. Of the former, each cubic centimeter contains 20 units; of the latter, each cubic centimeter contains 80 units. The concentration of sugar in the blood was determined by the method of Folin and Wu, and specimens of blood were obtained by direct puncture of the jugular vein.

Administration by Duodenum. The dog used for these experiments had been prepared 8 months previously, and was in excellent condition, weighing 11.2 kg. The animal had been maintained on the kennel diet and was fasted for 18 hours prior to each experiment. Determinations of blood sugar were made just prior to the administration of insulin, and at intervals of 30 minutes thereafter for at least 3 hours, and in most experiments for 6 hours. The insulin was injected directly into the duodenum through a small catheter as follows: (1) 200 units of insulin in a volume of 10 cc., washed in with an equal volume of water; (2) 200 units of insulin in a volume of 10 cc., mixed immediately before injection with 20 cc. of 0.2 per cent solution of hydrochloric acid; (3) 200 units of insulin in a volume of 10 cc. 1 minute after injection of 10 cc. of 0.2 per cent solution of hydrochloric acid and followed by a similar injection of acid after 3 minutes; (4) 200 units of insulin mixed with 100 cc. of normal dog serum, and (5) 200 units of insulin mixed with 100 cc. of citrated normal dog blood. The determinations of blood sugar need not be given in detail since none deviated from the normal values previously determined for the dog concerned. Injection by the foregoing methods of larger amounts of more concentrated insulin, 400 to 800 units of insulin, of which each cubic centimeter contained 80 units, produced definite lowering of sugar of the blood. Within 30 minutes the concentration of blood sugar was reduced from 40 to 50 mg. for each 100 cc. and returned to normal in from 1 to 4 hours. Symptoms of hypoglycemia were not produced.

Administration by Jejunum. This dog had been prepared 2 months previous to the experiment. A catheter passed through the exposed loop of intestine entered the jejunum 20 cm. below the ligament of Treitz. The animal was in good condition and weighed 4.5 kg. The animal had been on the standard kennel diet and was fasted 18 hours prior to each experiment. The insulin was injected directly into the jejunum as follows: (1) 100 units of insulin in a volume of 5 cc., washed in with an equal volume of water; (2) 100 units of insulin mixed immediately before injection with 10 cc. of 0.2 per cent solution of hydrochloric acid; (3) 100 units of

insulin together with 50 cc. of normal dog serum, and (4) 100 units of insulin together with 50 cc. of citrated normal dog blood. Determination of blood sugar taken at intervals of 30 minutes for at least 3 hours after administration of insulin did not disclose deviation from the normal values for blood sugar previously obtained in the animal. Injections of larger amounts of more concentrated insulin were effective in reducing the sugar of the blood to about the same extent as when the insulin was injected into the duodenum.

Administration by Ileum. This dog had been prepared 8 months previous to the experiment. A catheter passed through the exposed loop of intestine entered the ileum about 70 cm. from the cecum. The animal was in good condition and weighed 11.2 kg. It had been maintained on the standard kennel diet and was fasted 18 hours previous to each experiment. The insulin was injected directly into the ileum as follows: (1) 200 units of insulin in a volume of 10 cc. washed in with an equal volume of water; (2) 200 units of insulin in a volume of 10 cc., preceded by and followed by injection of 10 cc. of 0.2 per cent solution of hydrochloric acid; (3) 200 units of insulin in a volume of 10 cc., mixed immediately before injection with 20 cc. of 0.2 per cent solution of hydrochloric acid; (4) 200 units of insulin in a volume of 10 cc., together with 100 cc. of normal dog serum; (5) 200 units of insulin in a volume of 10 cc., together with 100 cc. of citrated normal dog blood, and (6) 200 units of insulin in a volume of 10 cc. together with 20 cc. of bile from the gall bladders of normal dogs. Determinations of the blood sugar, made every 30 minutes for at least 3 hours after administration of insulin, did not show appreciable deviation from the normal values previously obtained in the animal. The administration of insulin with blood serum and with blood were all complicated by the fact that the animal began to pass the injected blood or serum by rectum 1 hour and 15 minutes after administration, and in every experiment some blood or serum was passed within 2 hours after administration. Injections of larger amounts of more concentrated insulin were effective in reducing the sugar of the blood, but were less effective than duodenal injections of the same amount.

Administration by Isolated Ileac Loop. One dog used in this experiment had been prepared 4 years previously. In dogs with isolated ileac loops of only a few weeks' duration results were similar. The isolated loop consisted of about 30 cm. of ileum, both ends of which were open on the surface of the abdominal wall. The animal was in good condition, weighing 17.4 kg.; it had been fasted for 18 hours. Insulin was slowly instilled into the proximal end of the isolated loop, so that no leakage occurred; 30 minutes were taken for each injection. One hundred units of insulin in a volume of 5 cc. were instilled under the following conditions: (1) Without previous washing of the isolated loop; (2) following washing of the isolated loop with 50 cc. of water; (3) following washing of the loop

with 50 cc. of 0.1 per cent solution of hydrochloric acid; (4) following addition of strong hydrochloric acid to the insulin, so that the solution contained 0.2 per cent of hydrochloric acid, and (5) after addition of 2 cc. of bile from the gall bladder. All of these experiments were satisfactory except the administration with bile. This stimulated secretion in the loop so that the volume increased rapidly, and considerable of the solution was expelled. Determinations of blood sugar taken at intervals of 30 minutes after administration of insulin were all within normal limits. Only one experiment might be regarded as doubtfully significant. After the loop had been washed with 50 cc. of water, 100 units of insulin in a volume of 5 cc. were instilled into the loop in 25 minutes. The concentration of blood sugar before insulin was administered was 108 mg. in each 100 cc., and the readings at intervals of 30 minutes thereafter were 98, 78, 108, 99, 98, 91, 98, 91 mg. Repetition of this experiment did not alter the blood sugar even to this extent, and repeated instillations of 100 units of insulin every 30 minutes for 2 hours was ineffective. Insulin in more concentrated solution caused definite lowering of the sugar of the blood, but symptoms of hypoglycemia were not produced.

The following experiment also was performed on a dog with an isolated intestinal loop. It demonstrates the effect of insulin absorbed into the mesenteric veins. Seventeen and five-tenths units of insulin were injected through a fine needle submucously into the exposed ends of the intestinal loop. Not more than 2 units were injected at one time, and 25 minutes elapsed during the injections. Some leakage occurred at the sites of injection so that the amount actually injected was less than 17.5 units. The concentration of blood sugar was 116 mg. in each 100 cc. when the injections were begun. Five minutes after completion of injections the concentration of blood sugar was 63 mg.; 50 minutes after injection, 51 mg.; 1 hour and 20 minutes after injection, 44 mg.; 1 hour and 50 minutes after injection, 46 mg.; 2 hours and 50 minutes after injection, 62 mg., and 3 hours and 50 minutes after injection, 86 mg.

That the mucosa of the isolated loop was not completely impervious to substances in solution was demonstrated by the following experiment: 6 mg. of phenolsulphonephthalein, in a volume of 1 cc., was instilled into the proximal end of the isolated intestinal loop. One hour later the urine contained 30 per cent of the injected phenolsulphonephthalein and in the next hour 10 per cent was recovered. At the end of this period the mucosa of the isolated loop was still deeply stained.

That insulin does disappear from the contents of an isolated ileac loop is shown by the following experiment: After preliminary washing of the isolated ileac loop with water, 100 units of insulin in a volume of 5 cc. were instilled into the loop. One hour later

the loop was washed twice with 5 cc. of water; the entire volume of water was recovered. No change was produced in the sugar of the blood of this animal. The insulin from the ileac loop, washed out after 1 hour, was then injected subcutaneously into a dog weighing 5.1 kg. The sugar of the blood at the time of injection was 85 mg. in each 100 cc. and at intervals of 30 minutes afterward was 74, 47, 52, 54, 72, 84, and 86 mg. in each 100 cc. Thus it is seen that sufficient insulin remains after having been 1 hour in the loop to produce a definite decrease in the blood sugar of an animal after subcutaneous injection. It is clear, also, that about 90 per cent of the insulin instilled in the intestinal loop had disappeared within an hour.

If destruction of insulin was caused by enzymes within the lumen of this portion of bowel, it was considered that comparable destruction should occur if the washings of this loop were incubated with insulin. One hundred units of insulin in a volume of 5 cc. were instilled into an isolated ileac loop which had not been washed for several days. Five minutes later this was washed out with 6 cc. of water; a small portion of the washings was unavoidably lost. The entire volume of recovered fluid was 6 cc., which was incubated at 37° C. for 1 hour and 30 minutes. The entire solution was then injected subcutaneously into a dog weighing 6.6 kg. At the time of injection the blood sugar was 83 mg. in each 100 cc. and at intervals of 30 minutes following it was 65, 58, 52, 52, 50 and 45 mg. at which time hypoglycemic convulsions occurred. The animal recovered immediately after intravenous injection of 15 gm. of glucose but later died of hypoglycemia. This experiment indicates that little enzymatic substance capable of rapidly destroying insulin is present within the isolated ileum.

Comment. Experiments on animals with a loop of ileum isolated from the remaining portions of the gastrointestinal tract failed to show evidence of effective absorption of insulin, but these experiments appear to be more instructive. With the demonstration that insulin injected submucously in the ileum is of approximately similar effect to that injected subcutaneously in producing decrease in the sugar of the blood, it would appear that any appreciable absorption from the mucosa, or unaltered insulin, would likewise decrease the sugar of the blood. Since washings from the loop of ileum 1 hour after instillation of insulin produced definite lowering of the concentration of glucose in the blood of dogs following subcutaneous injection of these washings, one is justified in assuming that all of the insulin was not destroyed within the loop. From a quantitative standpoint it appears that about 90 per cent of the insulin instilled in the loop of ileum disappears within an hour. The sugar of the blood was not altered by the large amount of insulin that disappeared. It must have been destroyed either within the lumen of the intestine or within the mucosa. If enzymes secreted into the

lumen of the bowel destroyed insulin rapidly, washings from this portion of the intestine should destroy insulin when incubated with it. Experiments showed that insulin was not rapidly destroyed by incubation after having been washed through a portion of the ileum. It would appear that insulin is destroyed by the mucosa of the intestine. The effectiveness of concentrated insulin appears as evidence that the intestine is not impervious to this substance, and also indicates that the inactivation of insulin by the mucosa of the intestine may be incomplete if absorption is sufficiently rapid.

From the work of Fisher, and Fisher and Noble, one might possibly conclude that the insulin is not destroyed by the intestine but that it may be inactivated and excreted by the kidneys. They found that insulin administered by a Thiry fistula lowered the blood sugar of depancreatized dogs and of normal puppies, but that it was without effect on normal dogs. Large amounts of insulin were recovered in the urine following the enteral administration of insulin to normal and to diabetic dogs.

It should be emphasized that in all of our experiments normal dogs were used and that any conclusions concerning the action of the intestine on insulin must necessarily refer only to normal tissues. It is possible that in pathologic conditions such as diabetes, alterations in the permeability of various tissues may be present.

Summary. Large amounts of insulin may be instilled directly into the duodenum, jejunum or ileum without any appreciable effect on the sugar of the blood of normal dogs, except for the slight effects when concentrated insulin was used. The addition of acid, blood, or bile to insulin thus administered did not alter this. If insulin is injected into the lumen of an isolated portion of ileum the blood sugar of the animal is not affected, but small amounts of insulin given submucously produce typical hypoglycemia. Insulin gradually disappears from within the lumen of the ileum. With the doses we have used, sufficient insulin remains after 1 hour to produce definite hypoglycemia if injected subcutaneously. Insulin incubated with ileac washings is not so rapidly destroyed. It would appear that the intestinal mucosa inactivates insulin so that it is not effectively absorbed. Small amounts of insulin may escape inactivation if sufficiently concentrated insulin is applied to the intestine.

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THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF CORONARY OCCLUSION BY THE USE OF CHEST LEADS.

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MANY cases of coronary occlusion do not show characteristic changes in routine electrocardiogram. It seems that there are "silent areas" in the heart where infarction may occur without producing a deviation of the S-T interval from the isoelectric line in any of the three conventional leads. During some recent animal experimentation¹ we found that typical electrocardiographic evidence of cardiac infarction could be recorded after occlusion of arteries supplying hitherto silent areas. To do this it was necessary to depart from the three conventional leads and to lead the cardiac action currents to the galvanometer from new points. Shortly after these experiments were completed a patient presented herself with a clinical picture typical of coronary occlusion, but with no electrocardiographic indications of the presence of such a lesion. (Fig. 1-A, Leads I, II and III.) We, therefore, departed from the three conventional leads, applied the electrodes to the anterior and posterior surfaces of the chest wall and obtained striking deviations in the S-T interval from the isoelectric line. (Fig. 1-A, Lead IV.) The results obtained in this case and in another subsequent one (Fig. 2) make it apparent that the anteroposterior chest lead (Lead IV) is an important adjunct to the routine electrocardiogram

in the diagnosis of certain cases of coronary occlusion. Craib² has discussed the "silent areas" in the heart and has outlined the reasons for their failure to affect the electrocardiogram taken from the conventional three leads. Chest leads have been employed by various investigators for many years in the study of the heart. Waller,³ in his original work with the capillary electrometer, in 1887, placed his electrodes directly on the chest wall. Lewis has used this method repeatedly since 1909,⁴ especially in his studies of the mechanism of auricular action. However, so far as we are aware, chest leads have not been employed hitherto for the clinical study of cardiac infarction. Certainly, if they have been, the results are not commonly known.

Case Reports. CASE 1.—M. K., a white female, aged 76 years, was admitted to the Hospital of the University of Pennsylvania (Dr. Stengel's service) on September 14, 1931. She had had mild diabetes for at least 7 years, and was known to have had a slight elevation of blood pressure (160 systolic and 90 diastolic) before the onset of the present illness. In other respects her past medical history is irrelevant. She had been enjoying her usual state of health until September 1, 1931, when, while walking on the street, she was seized with a severe paroxysm of pain in the precordium and epigastrium, accompanied by a feeling of suffocation. She collapsed in a nearby drugstore. The attack lasted 20 minutes and then disappeared completely, leaving only a sense of fatigue. A second attack occurred after she had eaten her supper on September 5. It was similar to the first and lasted 10 minutes. On September 12, at 11.30 p.m., when the patient was in bed, a third attack of pain seized her. It was similar in location to the other two, but it was much more severe and lasted for 5 hours. Morphine was required for relief. The blood pressure at that time was 180 systolic and 100 diastolic. A fourth attack occurred at 7 a.m. on the day of admission to the hospital, September 14. It was the most severe of all and lasted until the patient had been quite heavily narcotized with morphine at 11 a.m. A definite soreness of the precordium continued for more than 24 hours.

Physical examination on admission showed an elderly white woman with a temperature of 97° F., a pulse rate of 100 and a respiratory rate of 22 per minute. She appeared acutely ill. She was restless and slightly cyanosed. There was an odor of acetone on her breath. There was definite tenderness over the precordium. The heart was not demonstrably enlarged. The cervical veins were not engorged. The heart sounds were regular and of normal intensity. No murmurs were heard. There were crackling râles at the lung bases. The abdomen was distended. The liver was not palpable. There was no edema of the feet or sacrum.

Diagnosis. The patient's history and examination suggested the diagnosis of coronary occlusion.

Course. This diagnosis was born out by the subsequent course of events: (1) There was a rise of temperature to 101° F. for several days, then a gradual subsidence. (2) The leukocyte count was 16,000 on September 14, 14,000 on September 17 and slowly decreased to 9800 on September 28, 1931. (3) Although there was no acute shock on admission (blood pressure, 155 systolic and 90 diastolic), by the next day, September 15, the pressure had fallen to 110 systolic and 60 diastolic. It then began to rise slowly, reaching 130 systolic and 90 diastolic on September 18, and has fluctuated in that region ever since. (4) A definite friction rub was heard

at the apex on September 16. It disappeared the next day. (5) There was a moderate degree of tachycardia (90 to 110) for several days after admission. The rate subsided to 75 during the course of the next 2 weeks. (6) Definite signs of congestion developed at the lung bases, persisted for 10 days and then cleared up gradually.

The patient's diabetes and acidosis were promptly controlled with glucose, insulin and dietary measures. Dysuria and abdominal distention were troublesome, but finally yielded to treatment. The patient made a tardy recovery. At the present writing, October 25, 1931, she is apparently well on the road to a healing of her infarct but she still remains weak and incapacitated for any exertion.

The *electrocardiographic studies* constitute the center of our interest in this case. Tracings were taken daily from the day of admission, September 14, until September 19, then every other day until October 2, 1931. Since then they have been made at intervals of 4 to 6 days. The three conventional leads were taken with the patient in the semirecumbent position in bed. In addition, a chest lead was used. (This lead has been designated Lead IV for the sake of convenience.) The following method was employed: Pads moistened in warm saline were placed over the front and back of the chest, approximately at the cardiac level, just to the left of the midline. The ordinary German silver electrodes were placed over these pads. The anterior electrode was connected to the right arm lead wire. The posterior electrode was connected to the left arm lead wire. A simple method of holding the electrodes snugly in place was found to be the use of a $\frac{3}{4}$ -inch rubber tube stretched fairly tightly around the chest over the electrodes and clamped at the ends with a hemostat. It is vital to have the resistance low, and to standardize the string accurately. Overshooting may produce changes in the electrocardiogram of normal individuals, which might be confused with significant *S-T* interval deviations. Rubbing the skin with alcohol, burnishing the electrodes and keeping the pads hot and closely applied to the skin are the main precautions necessary to prevent overshooting.

The following three points are brought out by the tracings (Fig. 1): (1) The progressive changes which took place in Leads I, II and III during the course of the first 4 weeks suggest the diagnosis of coronary occlusion. (2) Of all the 20 tracings taken from time to time by the three conventional leads, no single tracing gave any indication of the presence of a myocardial infarct, except possibly that taken on September 18, 1931. (Fig. 1-B.) Even in this tracing the *R-T* interval elevation did not exceed 1.5 mm. (3) Lead IV (the chest lead) gave unmistakable diagnostic information the very first day and continued to do so for 8 days after the infarction. From the eighth to the sixteenth day the evidence was less definite, but certainly suggestive. The marked depression of the *S-T* interval, which was present during the first week subsequently gave place to an upright *T* wave.

CASE 2.—A business man, aged 62 years, was apparently well until October 3, 1931. That night he had a brief attack of pain in the left side of the neck and precordium. On October 5 at 8.30 p.m., while walking home he was seized with a very severe pain also located in the neck and precordium. He was barely able to reach home. His physician, Dr. C. I. Ulmer, was immediately summoned. The pain persisted for 2 hours despite the prompt administration of morphin. On October 8 the patient had a second severe attack, lasting 2 hours, also requiring morphin for relief. Since then he has had no more actual pain. However, during October 15 and October 16 he was very badly bothered with a great deal of gas in his stomach.

He was first seen by one of us on October 17, 1931. He had a slight fever (99° F.) and a moderate leukocytosis (13,000) until October 24.

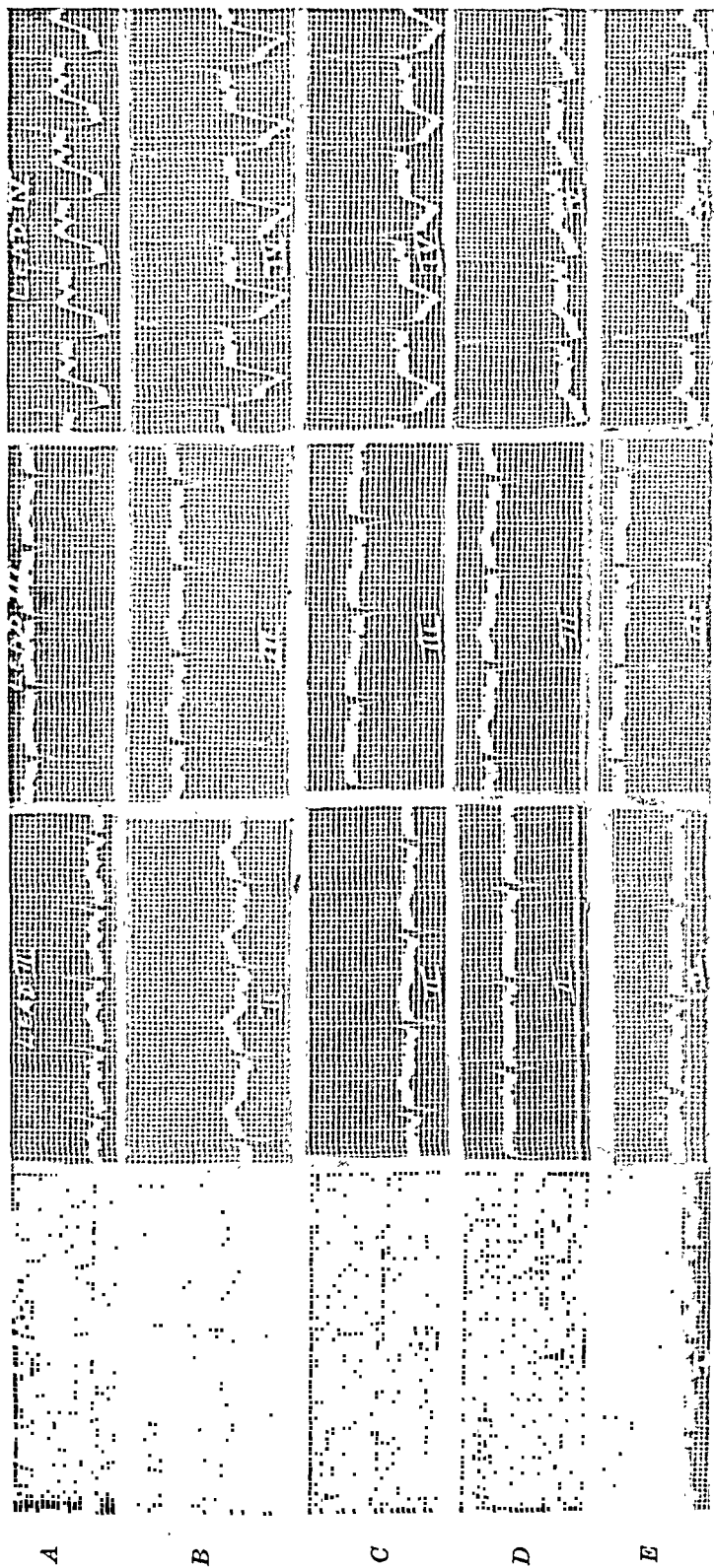


Fig. 1.—Case 1. A. Severe attacks of pain had occurred on September 12 and September 14, 1931. This tracing was made shortly after the subsidence of the attack on the latter date. Leads I, II and III do not suggest the presence of a recent myocardial infarct. Lead IV shows an *S-T* interval depression of 6 mm. B. Tracing taken September 18, 1931, four days after the last attack of precordial pain. There was still a slight leukocytosis (13,000). The temperature was still somewhat elevated. Lead I shows an *R-T* interval elevation of 1.5 mm. This is the only finding suggestive of coronary occlusion which was found in any single tracing taken with the three conventional leads. Lead IV shows an *S-T* interval depression of 5 mm. and a deeply inverted *T* wave. C. Tracing taken, September 21, 1931. The general condition of the patient had improved considerably by this time. There was still a leukocytosis of 11,000. The temperature reaction had practically subsided. The first three leads show no phenomena suggestive of coronary occlusion. Lead IV still shows an *S-T* interval depression of 2.5 mm. and a deeply inverted *T* wave. D. Tracing taken, September 30, 1931. The patient was afebrile and had a leukocyte count of 9300. Her general condition had improved markedly. The *T* wave in Lead I is beginning to show inversion. Lead IV still shows a depression of the *S-T* interval. A slight amount of overshooting in this tracing renders measurement of this abnormality inaccurate. The *T* wave in Lead IV is beginning to become upright. E. Tracing taken, October 16, 1931. Patient convalescing satisfactorily. Minor changes have appeared in Leads I, II and III. Lead IV shows an *S-T* interval depression of 1 mm. and a definitely upright *T* wave. This latter finding constitutes an abnormality in Lead IV. The progressive changes manifested in these tracings from day to day constitute strong presumptive evidence of coronary occlusion.

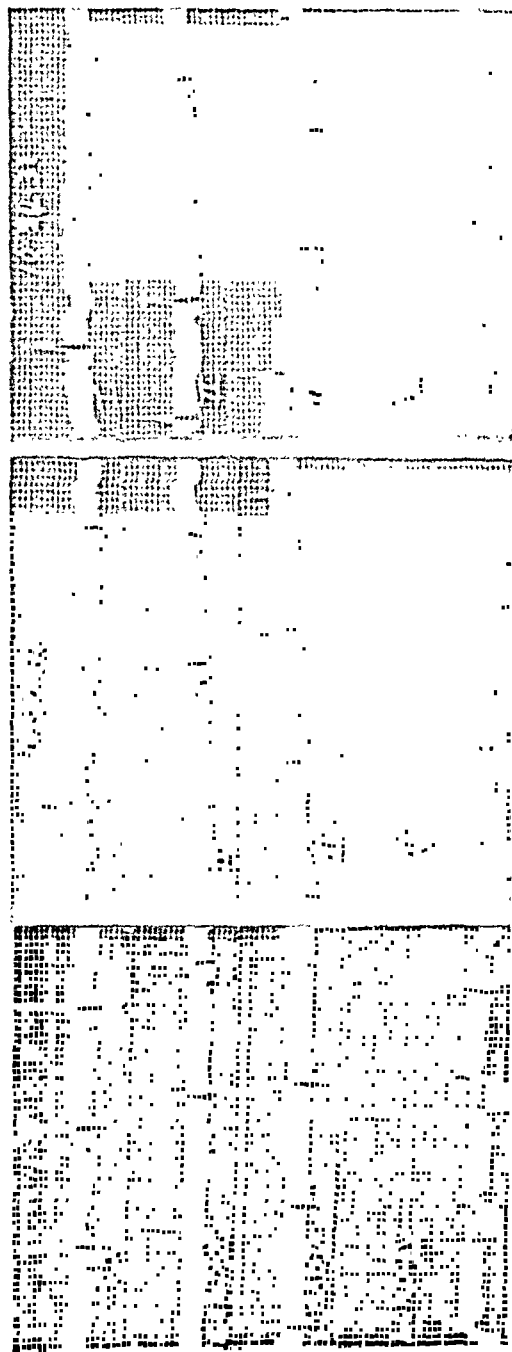


FIG. 2.—Case 2. A. Tracing taken, October 18, 1931. Severe attacks of pain had occurred on October 5 and October 8. There had been no definite evidence of an extension of the infarction since the latter date, although there was a fever of 99.3° F. and a leukocytosis of 13,000 when this tracing was taken. The contours of the R-T interval and T wave in Lead I suggest the diagnosis of coronary occlusion. Lead IV shows an S-T interval depression of 3 mm. B. Tracing taken, October 20, 1931. The febrile reaction was still present. There is practically no suggestion of coronary occlusion in Leads I, II and III. Lead IV shows an S-T interval depression of 2 mm. C. Tracing taken, October 24, 1931. The febrile reaction had begun to subside. The leukocyte count was 9000. The T wave in Lead I shows beginning inversion. The contours of the S-T interval and T wave suggest the diagnosis of recent myocardial infarction. Lead IV shows a depression of the S-T interval of 3 mm. The progressive changes which have occurred in the contour of the ventricular complex, especially in Lead I, are presumptive evidence of coronary occlusion.

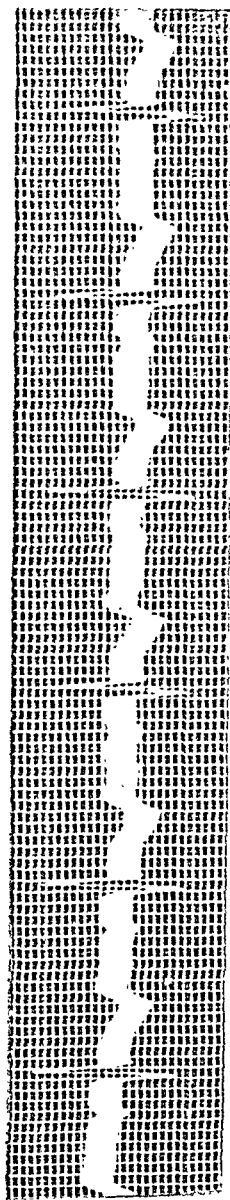


FIG. 3.—The normal contour of Lead IV—the anteroposterior chest lead. The P wave is usually inverted, a Q wave is generally present and the T wave is inverted.

His blood pressure was 130 systolic and 70 diastolic. (It had been recorded at 160 systolic a few weeks prior to the present illness.) There was slight cyanosis of the lips and nail beds. The heart sounds were normal and not unduly rapid. There was no pericardial friction, and no evidence of circulatory failure. He had a brief, mild pain in the throat on October 18, somewhat similar to the more severe pains referred to above. Since then he has had no suggestion of cardiac pain.

The *electrocardiographic studies* of this patient are shown in Fig. 2. The following facts are brought out: (1) The progressive changes in the tracing are highly suggestive of a recent coronary occlusion. (2) The appearance in Lead I, when considered in conjunction with the clinical picture, practically establishes the diagnosis of myocardial infarction. (3) As in Case 1, Lead IV shows the most striking electrocardiographic phenomena (a 3-mm. *S-T* interval deviation).*

Thirty-three controls (20 normals and 13 patients with cardiovascular disease) have been studied by means of Lead IV. The normal tracing in this lead is illustrated in Fig. 3. The *P* wave is often inverted. The *Q-R-S* complex is often of higher voltage than that seen in the other three leads. There is usually a deep *T* wave. The *T* wave is inverted.† Deviations of the *S-T* interval from the isoelectric line were not seen in this group. We presume that when *S-T* interval deviations appear in Lead IV they probably have the same significance as when they occur in the three conventional leads. That is, they are nearly, but not quite, pathognomonic of myocardial infarction.⁵

Comment. Apparently Lead IV will bring to light infarcts in areas hitherto electrocardiographically silent. Probably there are no truly "silent areas" in the heart. An infarct of appreciable dimensions‡ will probably always produce a recordable change in the action current of the heart, no matter where it is situated. The reason why certain parts of the heart muscle do not affect the routine electrocardiogram is probably because the axes of our conventional leads have not been suitably placed to record changes in the action current in these areas.² It is possible, therefore, that other chest leads besides Lead IV may occasionally be useful.

It is possible that Lead IV may find a place in routine electrocardiography. It would seem logical to use it, since it appears to give information concerning the condition of parts of the heart muscle which do not produce effects on the routine electrocardiogram which we are able to recognize as significant. In certain of our controls with cardiac damage we found *T* waves opposite in sign to the normal.

If conclusions are to be drawn from minor daily variations in

* Follow-up examination on November 27, 1931: the *S-T* interval in Lead IV had returned to the isoelectric line; the *T* wave was +4 mm. Recovery had been uneventful and satisfactory; *T*₁ was -3 mm., *T*₂ was +1.5 mm., *T*₃ was +4 mm.

† An inverted mirror image of this tracing with no *Q* wave and an upright *T* wave can be produced by reversing the lead wires.

‡ The exact size of an infarct necessary to produce a detectable change in the electrocardiogram taken from the surface of the body has not been determined.

the contour of the tracing in Lead IV the relation of the electrodes to the heart should be kept constant. We paid no attention to minor variations in the position of the electrodes and have not drawn conclusions on these grounds.

Changes of so-called "specific" nature have been noted in 50 per cent of attacks of angina pectoris.⁶ It is possible that the incidence of "specific" changes might be greater if four leads were used instead of three.

Barnes and Whitten⁷ have shown that it is often possible to localize a myocardial infarct by means of the electrocardiograph. Lead IV should assist materially in accomplishing this. In the light of the results of our animal experimentation we would expect an anterior infarct to produce an *S-T* interval depression in Lead IV, whereas a posterior infarct should produce an *R-T* elevation.* According to this hypothesis, we suspect that both of our patients suffered infarction of the anterior wall of the left ventricle. This suspicion is strengthened by the electrocardiographic phenomena in Leads I, II and III. The expected subsequent development of a *T* wave of the opposite sign was noted in Case 1. A final evaluation of the usefulness of Lead IV in the localization of myocardial infarcts will necessarily await combined electrocardiographic and necropsy study of a series of cases.

Summary and Conclusions. Two cases are reported to illustrate the use of Lead IV (an anteroposterior chest lead) in the electrocardiographic diagnosis of coronary occlusion. In Case 1 the three conventional electrocardiographic leads yielded little or no diagnostic information except on the fourth day. Nevertheless, for 8 days after the original infarction Lead IV showed striking and unmistakable deviation of the *S-T* interval from the isoelectric line. In Case 2 both Leads I and IV showed evidence of coronary occlusion. Lead IV showed a much more striking *S-T* interval deviation than was seen in Lead I.

In a series of 33 controls deviation of the *S-T* interval from the isoelectric line was not seen. When *S-T* interval deviations appear in Lead IV they probably have the same significance as when they occur in the three conventional leads.

The employment of chest leads adds materially to the usefulness of the electrocardiograph in the study of certain cases of myocardial infarction. When the three conventional leads show no evidence of coronary occlusion, Lead IV may show striking deviations of the *S-T* interval from the isoelectric line.

It is apparent that certain of the areas of the myocardium which are "silent" in the three conventional leads have a definite effect on Lead IV.

The usefulness of Lead IV in routine electrocardiography and in the location of myocardial infarcts is discussed.

* These statements apply only if the lead wires are attached as specified above.

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AURICULAR FIBRILLATION.

ITS ETIOLOGY, AGE INCIDENCE AND PRODUCTION BY DIGITALIS THERAPY.

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HEART failure is associated so frequently with auricular fibrillation that the relationship between the two is now clearly established. The *modus operandi* of this relationship is not, however, clear, and this point, along with certain prognostic considerations, has been the subject of much speculation. Despite a number of excellent statistical reports upon the subject of auricular fibrillation, several important points have not been emphasized. Among the latter can be included the great rarity of auricular fibrillation in the various forms of syphilitic heart disease, the age incidence of the arrhythmia and the production of auricular fibrillation as a result of too enthusiastic administration of digitalis and its products. An attempt will be made in this paper to illustrate these points by a review of the material collected in The Johns Hopkins Hospital.

Since the publication of Mackenzie's²⁴ original observations many authorities have confirmed the fact that fibrillation of the auricles is almost the rule when a heart, crippled by mitral stenosis, is no longer able to meet the demands of the circulation. It is also known that

auricular fibrillation is rare in disease of the aorta or of the aortic valves. In Lewis¹⁸ series of 152 cases of auricular fibrillation 51.5 per cent had mitral stenosis and but 5.9 per cent had aortic valvular disease while 46.7 per cent gave a history of rheumatic fever or chorea and but 0.7 per cent had a history of syphilis. In the series of 359 cases reported by Brachman² 37 per cent had mitral stenosis, 37 per cent "appeared to be primary myocardial" and 1.4 per cent had aortic disease alone. Cookson's⁹ 361 cases, seen at the London Hospital, were distributed as follows: post-rheumatic heart disease 69 per cent, nonrheumatic heart disease (including the instances of hypertension and arteriosclerosis) 22 per cent, exophthalmic goiter 7 per cent and syphilitic aortitis 2 per cent.

A study has been made of the records of 575 patients seen here during the past 12 years in whom the electrocardiograms have at one time or another shown auricular fibrillation. This series embraces all the instances of auricular fibrillation recognized among the electrocardiographic records of the hospital during that period.

Etiology. From the clinical notes and from the necropsy protocols, when such have been available, the cases have been divided into groups, according to etiology, as indicated in Fig. 1.

Patients with rheumatic heart disease (mitral stenosis alone or in combination with other valvular lesions) constituted the largest single group—forming 34.4 per cent of the total number. The "arteriosclerosis" group, comprising 31.1 per cent of the total, contains those elderly individuals with generalized arteriosclerosis in whom the systolic blood pressures at the time of examination were not above 150 mm. of mercury.* In the "hypertensive" group are included those cases in which the systolic blood pressures were above 150 mm. of mercury (a purely arbitrary figure). In some cases arteriosclerosis or renal disease was also present. Under the heading of "emphysema" are grouped those patients in whom the conspicuous abnormality appeared to be chronic bronchitis, emphysema or fibroid pulmonary changes of long standing. A certain degree of arteriosclerosis was of course present in the majority of the latter cases as they fell in the later decades of life. It is of particular interest that auricular fibrillation was associated with syphilitic cardiovascular disease in but 3 per cent of the total series. This point will be discussed more fully later.

Age Incidence. The age incidence of auricular fibrillation corresponds closely to that of myocardial insufficiency resulting from rheumatic and degenerative forms of heart disease. The percentage occurrence in various decades is dependent upon the type of clinical cases encountered, and is, therefore, not strictly comparable in different series. Some authors note the age at onset and others

* Cookson⁹ uses the term "nonrheumatic" rather than "arteriosclerotic" to characterize this group. Because of its questionable etiology it has been referred to in the French literature as the "primitive type."

575 CASES OF AURICULAR FIBRILLATION ARRANGED ACCORDING TO ETIOLOGY

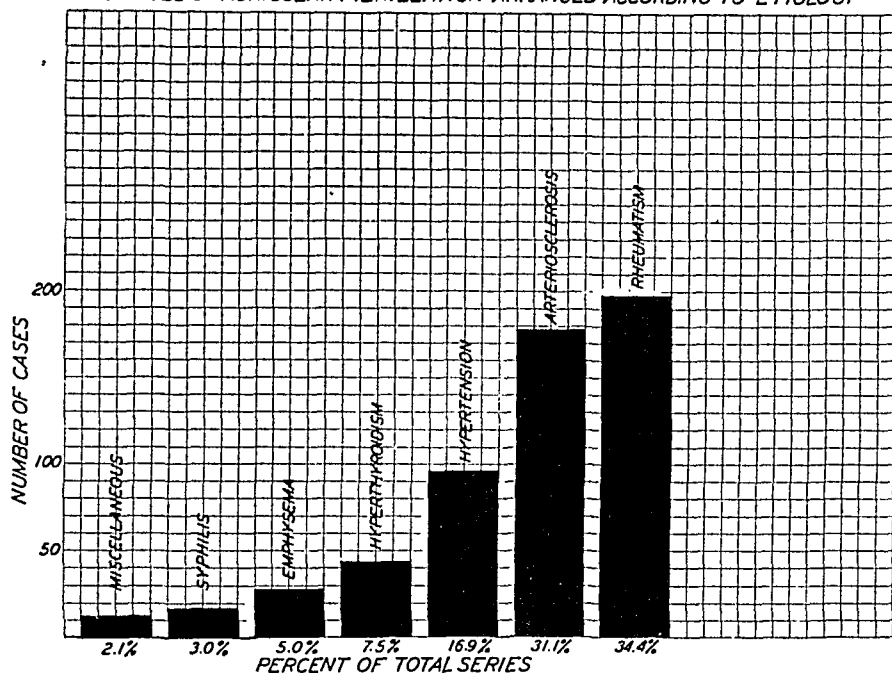


FIG. 1.—Shows the distribution according to etiology of 575 cases of auricular fibrillation.

575 CASES OF AURICULAR FIBRILLATION ARRANGED ACCORDING TO AGE GROUPS

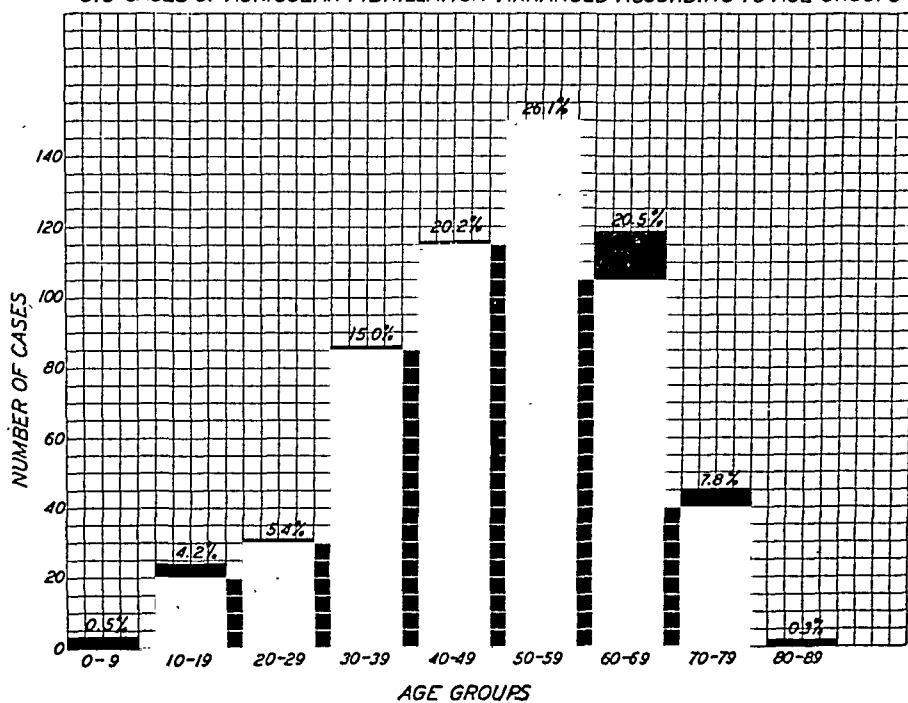


FIG. 2.—Shows the distribution in percentages according to age groups in 575 cases of auricular fibrillation.

the age at which auricular fibrillation was first recognized. In Mackenzie's²² series of 500 cases of auricular fibrillation the greatest incidence was in the decade from 56 to 66; in Willius'⁴⁰ 500 cases, between 51 and 60, and in Cowan and Ritchie's¹¹ series of 300 cases, between 40 and 49. The incidence of rheumatic heart disease, which tends to cause auricular fibrillation in the earlier decades, is rather high in the latter series. In 78 rheumatic cases recorded by Cookson⁹ the onset of auricular fibrillation occurred between the ages of 12 and 17 in almost one-third (23 cases).

In the present series, as will be seen by reference to Fig. 2, the highest incidence of auricular fibrillation was in the decade from 50 to 60.

Auricular Fibrillation in Childhood. Considerable interest has centered of late upon the incidence of auricular fibrillation in childhood. Examples of it are scarcely ever seen in the first decade, and the 3 instances in this series are therefore noteworthy. This figure probably represents fairly well the frequency of occurrence of the irregularity in a general hospital. Willius'⁴⁰ noted no case occurring in the first decade among his 500 cases and Cowan and Ritchie¹¹ no instance in 300 cases. In 1164 cases of auricular fibrillation at the London Hospital, Cookson⁹ found 30 (2.5 per cent) below the age of 17 and added 5 from other sources. In only 10 cases was there proof by graphic records. There was no instance occurring below the age of 12 years. Auricular fibrillation in Nadel's²⁷ case in a boy of 11 and in Neuhof's²⁸ case in a boy of 8 was the result of digitalis therapy although rheumatic heart disease was present in each. Two well-authenticated instances of auricular fibrillation occurring in the first decade have been recorded by Leys and Russell,²⁰ and Sutherland and Coombs³⁹ respectively; the first in a boy of 6 with questionable diphtheritic myocarditis and the latter in a boy of 5 with acute rheumatic fever. Cookson⁹ in 1929 was able to collect from the literature 13 instances in which auricular fibrillation appeared during the first 10 years of life; several of these cases are doubtful. Resnik and Scott³³ have recorded the youngest case of auricular fibrillation in the literature for which there is graphic proof. Their case was in a boy 4 years of age (Case 3 of our series), who had rheumatic heart disease. The other 2 cases are described briefly below.

Case Reports.—CASE 1. N.E., female, aged 8 years (H. L. H. 65378), was admitted to the hospital January 3, 1930, and died January 15, 1930. The child was well until the age of 6 when she developed scarlet fever which was followed by a rather severe attack of rheumatic fever and the family was told that the heart was "involved." Because of a general decline in health with weakness, fever, loss of weight and anorexia for a year she was admitted to the hospital. On admission there was slight fever, tachycardia, tachypnea, pallor, undernutrition, an enlarged heart with classical signs of mitral stenosis without signs of congestive heart failure. On the second day after admission without any other change of significance in her general

condition auricular fibrillation set in. She was then digitalized rapidly with a satisfactory drop in pulse rate but without restoration of normal rhythm. Finally a week after the onset, as congestive failure had not developed and as a totally irregular cardiac rhythm persisted, she was given 1 gm. of quinidin in divided doses over 16 hours. The administration of the drug was apparently accompanied by no untoward symptoms until a few minutes before death when the nurse noted that she was groaning and in much discomfort and before the house officer had arrived she died. A postmortem examination was not permitted.

CASE 2.—K. D., male, aged 8 (H. L. H. 57863), was first admitted to the hospital May 18, 1928, and died December 3, 1929. Postmortem examination revealed subacute rheumatic endocarditis involving all the valves and the endocardium of the left auricle, rheumatic myocarditis and chronic passive congestion of the lungs, liver, spleen and kidneys.

Fifteen months before entry he was ill for 3 months with severe rheumatic fever. Five months before entry the rheumatism recurred. On admission there was slight fever, emaciation, pallor, occasional choreiform movements, numerous subcutaneous fibroid nodules and signs over the heart that suggested mitral stenosis and insufficiency without congestive failure. An electrocardiogram revealed normal sinus rhythm. He did not do well but went home for short periods twice before the final admission. A year and a half before death, congestive heart failure became conspicuous and he was digitalized. From then until death heart failure and rheumatic infection progressed slowly. In September, 1929, he was admitted with well-marked heart failure and auricular fibrillation. For months he had been taking only maintenance doses of digitalis. After a week on quinidin the cardiac mechanism reverted to normal and remained so though he slowly grew worse and died December 3, 1929.

CASE 3.—Reported in detail by Resnik and Scott.³³

Schwartz and Weiss³⁸ studied 60 consecutive cases of rheumatic heart disease in children between 5 and 15 years of age who had been admitted to the Montefiore Hospital in New York. Auricular fibrillation was found in 10, at one time or another, and 4 of these were below 10 years of age. They maintained that this cardiac irregularity in young children was more frequent than is generally believed, and suggested that careful and continuous observation was necessary in order to recognize it. From the case histories it would seem highly probable that auricular fibrillation was brought on by digitalis in some instances. Certainly few observers would agree that the high incidence in the Montefiore series represented the usual experience.

The following table compiled by Cookson⁹ clearly indicates the grave prognosis that is associated with auricular fibrillation in childhood as compared to the later decades. c

THE EXPECTATION OF LIFE IN RHEUMATIC CASES WITH FIBRILLATION CLASSIFIED ACCORDING TO AGE OF ONSET. (AFTER COOKSON.)

Age at onset of fibrillation.	No. of cases.	Duration of life.
12 to 17	23	10.0 months
18 to 28	22	4.5 years
28 to 38	16	6.5 years
38 to 48	8	5.8 years
Over 48	9	4.1 years

This experience is illustrated in our 3 cases described above in which death occurred 10 days, 3 months and 10 months respectively after the onset of auricular fibrillation.

No attempt is made here to separate the instances of paroxysmal auricular fibrillation from those in which the arrhythmia was permanently established. Such a distinction is satisfactory only when the patient has been observed during an attack and later during a period of normal rhythm. Furthermore, a comparison of 200 cases of paroxysmal auricular fibrillation, reported by Parkinson and Campbell⁵⁰ with a similar group exhibiting established auricular fibrillation⁴ indicates that the different forms of cardiac disease occur in essentially the same percentages in each group. In the paroxysmal fibrillation as opposed to the permanent form, hypertensive heart disease displaces rheumatic heart disease as the commonest cause. Although "infective" or "toxic" causes may be arbitrarily placed in a separate group, in a consideration of the etiology of paroxysmal auricular fibrillation, it is well recognized that there is coexistent organic heart disease in most instances. It is safe to assume that auricular fibrillation, of either the transient or established form, seldom occurs in a perfectly normal heart.

Certainly paroxysmal auricular fibrillation frequently passes over into the established irregularity later and in many of these instances is ultimately shown to have an organic substratum. Parkinson and Campbell⁵⁰ have discussed this point in their scholarly review. The occasional exception to this rule must be recognized, however, and there appear to be a number of well-authenticated instances of paroxysmal auricular fibrillation occurring in the complete absence of any evidence of cardiac disease.

Paroxysms of auricular fibrillation, in the absence of evident heart disease, have been shown to result from many causes—drugs, infections, trauma, physical overexertion and numerous other factors. The literature on this subject is fully covered in the articles of Cowan¹⁰ and of Parkinson and Campbell.⁵⁰ Digitalis, the most important of the agencies referred to above, will be considered later.

Auricular Fibrillation in Syphilitic Cardiovascular Disease. The extreme rarity of auricular fibrillation in cardiac disease due to syphilis has been noted by a number of writers but is not a matter of common knowledge.* Carter and Baker⁶ have stressed the point in a recent paper⁹. Auricular fibrillation is so unusual in such

* Fibrillation of the auricles is rare also during the active stages of infective endocarditis,²⁵ in association with angina⁹ and in heart failure due to obstruction in the pulmonary circulation.²⁵ The low incidence of auricular fibrillation following coronary occlusion has been noted by Parkinson and Bedford.²⁹ Levine¹⁷ has shown that the percentage is in fact considerably higher. The high incidence (25 per cent of cases of coronary occlusion) observed in the latter series however has little bearing on the subject of permanent auricular fibrillation since in many instances the arrhythmia was temporary and was recognized only by continuous observation in the hospital.

instances that its presence militates strongly against the diagnosis of cardiovascular syphilis in a given case. The reason for this infrequent association is not apparent, unless it be dependent upon the fact that the damage in cardiovascular syphilis is limited to involvement of the aorta and aortic valve, the mitral valve and the myocardium usually being unaffected. Auricular fibrillation is also uncommon in disease of the aortic valve due to causes other than syphilis. Indeed it is less commonly met with in combined lesions of the aortic and mitral valves than in disease of the mitral valve alone. This vexed question of the ultimate cause of auricular fibrillation, although outside of the scope of the present report, will be discussed in brief, later.

In a series of 100 patients exhibiting heart failure with a *normal rhythm*³¹ cardiovascular syphilis was present in 21 per cent. On the other hand among Campbell's⁴ cases of auricular fibrillation only 2 per cent were associated with syphilitic cardiovascular disease. Similarly but 13 (2.6 per cent) of 499 instances of auricular fibrillation reported by Willius⁴⁰ were grouped under aortic insufficiency. No note was made of the etiology of the latter though syphilis was doubtless responsible in the majority of instances. Cowan and Ritchie,¹¹ over a period of 10 years, saw only 12 cases in which auricular fibrillation was associated with "aortic incompetence."

A positive blood Wassermann reaction was present in 8.6 per cent of Levine's¹⁶ series of 128 cases of auricular fibrillation. This rather high figure fails, however, to indicate the actual incidence of cardiovascular syphilis in his series, since aortic aneurysm was present in 2 instances, aortitis in 2 and "chronic myocarditis or chronic endocarditis and mitral stenosis or both" in 7 instances. Cohn,⁷ in quoting the older series of Frey (100 cases) and Semerau (111 cases), has noted that no cases of auricular fibrillation due to syphilitic cardiovascular disease occurred in the former group. Syphilis appeared to be the cause of the arrhythmia in 6.3 per cent of Semerau's cases. It should be noted, however, that 82 of the 111 cases in his series were drawn from military life.

In the present series auricular fibrillation was associated with syphilitic cardiovascular disease in only 3 per cent of the total number of cases. This is especially noteworthy for, due to the large number of negroes seen in this clinic, syphilitic aortitis is recognized as being present in 15.14 per cent of all patients admitted to the hospital with heart disease. The actual occurrence as proven at autopsy is even greater. A review of the records of those patients with cardiovascular syphilis who have exhibited a totally irregular rhythm has brought to light certain instructive facts.

There were 18 cases in this group or a little over 3 per cent of the entire series. At autopsy 1 of these patients had old rheumatic endocarditis with mitral stenosis, syphilitic aortitis with insufficiency of the aortic valves and a huge aneurysm of the aortic arch.

Autopsy in another case demonstrated that there was, in addition to syphilitic aortitis, an extensive arteriosclerosis of the pulmonary artery, probably syphilitic in origin. There was great hypertrophy and dilatation of the right ventricle. Two other patients were young women who at autopsy were shown to have syphilitic aortitis which did not involve the aortic valves. There was extensive myocardial scarring which would seem to be justifiably termed syphilitic myocarditis.* The coronary vessels were normal.

Induction of Auricular Fibrillation by Digitalis, Especially as Regards Syphilis. The remaining 14 syphilitic patients presented the classical picture of syphilitic aortitis with aortic insufficiency. Five of these had auricular fibrillation on admission which did not seem to be associated with any form of therapy. In the remaining 9 patients it appears probable that auricular fibrillation was associated with the administration of digitalis. Mackenzie²¹ pointed out, in 1911, that auricular fibrillation might result from effective doses of digitalis.† In an earlier report²³ such a case was described although the relationship was not clearly recognized. The single cases reported by Danielopolu,¹³ by Nadel²⁷ and by Neuhoof,²⁸ the 3 cases of Parkinson and Campbell³⁰ and the 2 of Schwartz²⁷ appear to be valid instances of this relationship. In 2 earlier cases reported by Schwartz²⁶ it seems likely that the attacks were precipitated by digitalis. The latter cases are of interest in that auricular fibrillation did not disappear until 4 to 6 weeks respectively after the drug had been discontinued. Some of the instances of auricular fibrillation in Schwartz and Weiss's²⁶ series of 10 cases in children were, as Cookson pointed out, almost certainly the result of digitalis administration.

In this group with cardiovascular syphilis, fibrillation of the auricles appears to have been induced by digitalis in 9 instances, 5 of which have already been reported by Resnik.²² In these 5 cases the strict criteria, suggested by Resnik as a basis for judgment upon the relationship between auricular fibrillation and digitalis therapy, were satisfied in every instance, to wit: (1) Absence of history of previous attacks of auricular fibrillation; (2) normal rhythm before administration of digitalis; (3) appearance of auricular fibrillation after a dose of digitalis shown, by clinical and electrocardiographic evidence, to be an effective amount; (4) persistence of the abnormal rhythm as long as digitalis is continued in doses sufficiently large to compensate for the elimination of the drug; (5) reestablishment of normal rhythm after discontinuance of the digitalis; (6) confirmation of the changes in rhythm by means of electrocardiographic records; (7) exclusion of other factors which tend to bring on transient auricular fibrillation.

Although such criteria are necessary to establish actual proof,

* The cases will be reported in full at a later date.

† Cushny¹² has produced the same phenomenon experimentally in animals.

there are frequent instances in which a patent relationship exists between digitalis therapy and the onset of auricular fibrillation, in which not all of these criteria can be satisfied. This is true of the remaining 4 cases in the group referred to above. These patients all had severe cardiac decompensation, and their electrocardiograms on admission showed normal sinus rhythm. After the administration of digitalis in large doses, clinical signs of the therapeutic effect of the drug were noted, auricular fibrillation ensued and the *T* waves of the electrocardiograms revealed changes that were attributed to the digitalis therapy. After the drug was discontinued, however, the cardiac rhythm in these 4 patients failed to return to normal during the period of our observation, (24, 17, 4 and 2 days respectively after the onset of auricular fibrillation).

It must be pointed out that although the 9 cases reported above fall into the group with cardiovascular syphilis, these cases are discussed merely to emphasize the rarity of auricular fibrillation in this form of heart disease and to illustrate the occasional occurrence of auricular fibrillation following excessive digitalis administration. It is not suggested that there is greater likelihood of digitalis giving rise to fibrillation in syphilitic cardiovascular disease than in other forms of heart disease with normal rhythm. Nor can such a conclusion be drawn from Resnik's series (5 out of 7 had cardiovascular syphilis) since his material was selected. Certainly digitalis was responsible for some of the instances in Schwartz and Weiss's series of auricular fibrillation in children with rheumatic heart disease. We have observed several instances of auricular fibrillation in patients with hypertensive heart disease in which the relationship to digitalis therapy satisfied all of Resnik's criteria. No study seems to be available bearing upon the relative liability to the induction of auricular fibrillation by digitalis in various types of heart disease with normal rhythm. It is possible that a careful analysis of records in all forms of heart disease would reveal more cases in which digitalis was responsible for the onset of auricular fibrillation.

The instances reported to date have been observed in patients exhibiting advanced heart failure and it would seem probable that a greater liability to fibrillation from digitalis exists under these circumstances. It must be remembered, however, that digitalis is usually administered in relatively large doses to such patients. Brams and Gaberman³ have recently completed a study in which digitalis was administered in large doses* to 9 patients without cardiac disease. Transient auricular fibrillation occurred in 1. We have observed the occurrence of fibrillation as a result of massive doses of digitalis in 1 patient with hypertensive heart disease who

* The usual amounts given were 45 cc. intravenously of potent digifolin over 9 days.

had but mild congestive heart failure. It would appear that in most instances, large doses of digitalis are required to produce the arrhythmia although it is possible that the customary doses may do so in susceptible individuals. Furthermore, although the instances of this relationship reported to date have developed in patients with congestive heart failure, the case noted above and that of Brans and Gaberman² show that the phenomenon may occur in the absence of severe congestive heart failure.

It is of interest to note that in auricular fibrillation, induced by digitalis, the ventricular rate is relatively slow. This is due to a coincidental "blocking" action of the drug through the vagus upon the bundle of His, as a result of which a smaller number of the irregular auricular impulses are able to reach the ventricle. Atropin, therefore, by releasing the vagus frequently causes a considerable rise in ventricular rate in such cases despite the fact that by its action on the auricular muscle it actually tends to slow the rate of circus movement to some extent. In 1 of the 7 patients to whom Resnik²² administered atropin, normal sinus rhythm was reestablished 68 minutes later apparently as a result of the atropin. A similar but less convincing case has been reported by Hering.¹⁵ The part played by the atropin is doubtful in both instances.

The onset of auricular fibrillation due to digitalis has been preceded in every instance by other evidences of digitalis intoxication, most frequently by the appearance of extrasystoles and coupled rhythm or more rarely by the development of nausea, vomiting, diarrhea and other concomitants of digitalis action. No instance has been noted in which the development of fibrillation seemed to have had any appreciable influence—either for better or for worse—upon the general clinical condition of the patient. After discontinuance of digitalis therapy normal sinus rhythm was usually reestablished within a few days. It is probable however, that harm would have resulted had the drug been continued and pushed still farther after the onset of fibrillation. Under such circumstances, ignorance of this point would tempt one to push digitalis in the hope of bringing about a normal rhythm whereas discontinuance of the drug would actually offer the best chance of obtaining this result. The latter is therefore not one of academic interest alone.

The Cause of Auricular Fibrillation. It is obvious that no one condition and no single set of circumstances can explain the development of auricular fibrillation in all cases. It appears to be a physiologic abnormality occurring most frequently in hearts that are damaged by disease. It has been observed, however, in individuals presenting no evidence whatever of cardiac damage and in such instances is usually of brief duration. In the latter cases there has been, without exception, some factor of infection, toxemia or overexertion that might conceivably have interfered with the normal metabolic processes of the heart. Excellent studies are available relating to the physiology of auricular fibrillation, to the morbid

anatomy of hearts from patients dying with the arrhythmia and to the clinical aspects of the subject. No comprehensive effort has been made however to link these phases together. Such a study would be well worth while.

Why does auricular fibrillation rarely occur in patients who die of syphilitic cardiovascular disease, while it is almost always present before death in the victims of rheumatic endocarditis? Why is the incidence of the arrhythmia lower in patients with combined involvement of the aortic and mitral valves due to rheumatism than in the instances of mitral disease alone? What is responsible for the frequent occurrence of auricular fibrillation in hyperthyroidism—a condition in which no significant organic lesion of the heart is demonstrable?²⁶ Why is fibrillation uncommon during the acute stages of rheumatic infection when one might suppose that involvement of the myocardium was at its height? These and many other questions remain unanswered. Brief reference to these problems has been made in the papers of Yater,⁴¹ of Robinson³⁴ and of Gossage and Hicks.¹⁴

In a consideration of the ultimate cause of auricular fibrillation, 3 obvious possibilities suggest themselves. First, that the normal processes of conduction within the auricles are disrupted as a result of morbid structural changes in the muscle fibers. That such a factor is of great importance is evidenced by the fact that the arrhythmia occurs in the vast majority of instances in individuals with organic heart disease. Many reports are now available, however, bearing upon the morbid anatomy of hearts from individuals who have exhibited auricular fibrillation during life. There is general agreement that no lesion can be found that is specific for or distinctive of the arrhythmia. Changes, when found, differ in no way from those observed frequently in the hearts of individuals who had normal rhythm during life. Conversely, in a number of instances of auricular fibrillation no pathologic changes whatever have been demonstrable in the hearts at autopsy. Yater⁴¹ has recently reviewed the literature and has published a large number of personal observations. The reader is referred to his paper for a full discussion of the subject.

In the second place the frequent occurrence of auricular fibrillation in hearts that are the seat of organic disease is susceptible of another explanation than the mere disruption of normal pathways of conduction in the auricles by structural areas of block. The nutrition and the metabolic processes of the auricular muscle in such circumstances must be profoundly altered. The occurrence of auricular fibrillation in apparently normal hearts following overexertion, hydrogen sulphid poisoning, induced hyperthyroidism, the anoxemia of pneumonia, alcoholic excesses, digitalis therapy and numerous other drugs and causes is evidence of the profound influence that may be produced by alterations in the metabolic activities of the heart. The long continued overwork and high auricular pressures

incident to mitral stenosis may produce changes in the nutrition of the auricular muscle of somewhat similar character.

Considerable experimental evidence lends weight to such a conception. Thus auricular fibrillation can be induced in animals, with ease by asphyxia. Similarly large doses of digitalis by direct action on the auricular muscle may bring on the arrhythmia even in perfused hearts. The stimulating paper of Carter, Andrus and Dieuaide² is illustrative of the fundamental changes that may occur in the development and propagation of the excitatory impulse in the heart as a result of anoxemia, alterations in the pH of the circulating fluid and similar factors. Such influences are even yet imperfectly understood when applied experimentally. It is entirely impossible at the present time to assess their significance in the production of auricular fibrillation in the human being.

The third factor—that relating to nervous influences is still largely of academic interest. Lewis, Drury and Bulger¹³ have called attention to the occasional occurrence of auricular fibrillation during vagal stimulation in experimental animals. Andrus and Carter¹ have shown that during vagal stimulation a single induction shock, introduced soon after the end of the refractory period, frequently produces auricular fibrillation. It is conceivable that in some instances conditions of increased vagal tone may play a part in the production of auricular fibrillation in the human.

It is impossible to state the relative importance of these three factors in the genesis of clinical auricular fibrillation. Any one or all three elements may be responsible in a given case. The final answer would appear to lie in further studies of the interrelationship between the cardiac arrhythmias and certain fundamental changes in the metabolism of the myocardium.

Summary. 1. A study has been made of 575 consecutive cases of auricular fibrillation confirmed by electrocardiographic records.

2. The etiologic relationships to the various forms of cardiac disease are tabulated.

3. The infrequent occurrence of the arrhythmia in the first decade of life is discussed and 2 additional instances are recorded.

4. Emphasis is laid upon the rarity of auricular fibrillation in syphilitic cardiovascular disease. In the present series, 35 per cent of cases were associated with rheumatic heart disease and only 3 per cent with syphilitic cardiovascular disease.

5. Note is made of the production of auricular fibrillation by administration of digitalis.

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THE ETIOLOGY, PROGNOSIS AND TREATMENT OF AURICULAR FIBRILLATION.*†

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THE subject of auricular fibrillation has occupied the attention of many notable workers, especially since 1909 when its relatively common incidence was first noted by Rotherberg and Winterberg¹ and by Lewis.² The inconsistency of its appearance in the various forms of cardiovascular disease, in fact even in the absence of any demonstrable cardiovascular damage, and the variable duration of life following its onset, have caused a general uncertainty as to its etiology, prognosis and treatment. The widespread impression that its occurrence foreshadows imminent death is in marked contrast to the number of patients in whom the duration of life after the onset of auricular fibrillation has been from 5 to 15 years. Is the answer to this inconsistency to be found in the etiology, age of onset or in the treatment of these cases? The published works of Paul White,³ Willis,⁴ Cohn⁵ and Jones⁶ have proved most interesting and have prompted us to examine our own series in the hope of throwing some further light on this subject.

The present series consists of some 253 cases treated in our

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private practice or in the wards or heart clinic of the Pennsylvania Hospital in Philadelphia. Only chronic fibrillators have been included, those having paroxysmal fibrillation or in whom normal sinus rhythm returned spontaneously have been eliminated. These cases have been followed over a period of at least 1 to 18 years after the onset of fibrillation. The diagnosis has been confirmed by electrocardiograms in each case. We have endeavored to discover first: Some universal cause; none has thus far become apparent. Second: Some standards by which to estimate the probable duration of life in cases of chronic auricular fibrillation. We have some definite impressions in this direction. Third: The most satisfactory method of treatment. In this we believe our observations are of definite value.

Etiology. In respect to etiology, we have divided our cases into those which were obviously of *rheumatic origin* and those of the "nonrheumatic" or so-called *arteriosclerotic* type. We have included in the rheumatic group those with a definite mitral stenosis even in the absence of a history of a typical arthritis accompanying rheumatic fever, chorea and "growing pains." We have not divided our so-called arteriosclerotic or "nonrheumatic" group into those with and without hypertension, although we realize the desirability of so doing. A third or miscellaneous group includes cases of thyrotoxic etiology, others presumably luetic, since they had manifestations of cardiovascular syphilis and, finally, those cases in which no etiologic factor was apparent. These three categories are comparatively well defined, although occasionally it is difficult to distinguish between cases of the arteriosclerotic and miscellaneous types. In them, however, we have been able to determine no factor which they share in common, either clinical or physiologic, which might account for the incidence of fibrillation. These cases differ in every apparent respect, including etiology, family history, occupation, age of infection, age of onset of fibrillation and degree of cardiac disability at the time of onset of the arrhythmia. There is apparently nothing to distinguish beforehand those cardiacs who will fibrillate from those who will not.

It will be seen here from Table 1 that of the 781 cases of cardiovascular disease admitted to the wards of the Pennsylvania Hospital during a period of 3 years auricular fibrillation occurred in 48 (25 per cent) of the 197 rheumatics, 52 (21 per cent) of the 247 sclerotics, and 38 (19 per cent) of the 199 with miscellaneous etiology. One may anticipate, therefore, that of the rheumatics, 1 out of every 4 patients will develop auricular fibrillation and of the others 1 out of every 5.

As to pathology, it has been well demonstrated by Yater⁷ from a comparative examination of 29 hearts which had previously fibrillated with a series of clinically similar cases which had not, that there is no characteristic pathologic difference. In fact, in

the arteriosclerotic group a greater degree of vascular sclerosis was frequently found in cases where fibrillation did not occur, while the fibrillators themselves often manifested practically no abnormal vascular changes. Our own findings lead us to agree with White,⁸ who states that "There is no pathology characteristic of auricular fibrillation."

TABLE 1.—INCIDENCE OF HEART DISEASE IN WARDS OF THE PENNSYLVANIA HOSPITAL OF PHILADELPHIA, FOR A 3-YEAR PERIOD.

	1928.	1929.	1930.	Totals.
With auricular fibrillation:				
Arteriosclerotic	16	15	21	52
Rheumatic fever	18	19	11	48
Syphilitic	4	2	1	7
Thyroid	2	3	1	6
Unknown	6	10	9	25
Total	46	49	43	
Without auricular fibrillation:				
Arteriosclerotic	78	67	102	247
Rheumatic fever	72	68	57	197
Syphilitic	42	35	38	115
Thyroid	0	1	1	2
Unknown	28	31	23	82
Total	220	202	221	
Total with and without auricular fibrillation	266	251	264	781

TABLE 2.—ETIOLOGY OF AURICULAR FIBRILLATION.

	No. of cases.	Rheumatics, per cent.	Total, per cent.
Rheumatic:			
Arthritis	73	59	
Chorea	3	2	
Arthritis and chorea	5	4	
Tonsillitis	17	15	
No history	24	20	
Total rheumatic fever	122	..	48.0
Arteriosclerosis	88	..	35.0
Syphilis	23	..	9.0
Thyroid	9	..	3.5
Miscellaneous	11	..	4.5
Total	253		

It will be seen from Table 2 that of our 253 cases 122 (48 per cent) were associated with rheumatic fever. Of these over one-half were of the arthritic type. The others, including chorea, tonsillitis and those which, due to the presence of mitral stenosis, we believe are of rheumatic etiology in spite of the absence of a definite rheumatic history. The arteriosclerotic group includes 88 (35 per cent). We agree with Cookson⁹ that the title of this group should probably be "nonrheumatic" rather than arteriosclerotic. Of the miscellaneous group, comprising 43 cases (17 per cent) of

the total, over one-half were associated with positive blood Wassermanns and definite clinical evidence of cardiovascular syphilis. The relationship of syphilis to auricular fibrillation is, at best, uncertain. Stokes¹⁰ states: "My impression has been that the more cardiovascular syphilis I have seen, the less auricular fibrillation; and the more auricular fibrillation, the less cardiovascular syphilis." In the recent reports from the Johns Hopkins Hospital¹¹ there was an entire absence of auricular fibrillation in a series of 100 cases of syphilitic cardiac disease. The small number of fibrillators with thyrotoxicosis, on the other hand, is not due to the infrequent complication of auricular fibrillation with goiter, but rather to the extremely low incidence of thyroid disease in the heart clinic and on the wards of the Pennsylvania Hospital.

It would appear, therefore, that while auricular fibrillation tends to occur consistently in a definite percentage of certain types of heart disease, its exciting cause is totally unknown. That the mechanism is one of abnormal conduction in the auricular muscle, as suggested by Garrey¹² and Mines,¹³ and recently supported by Lewis,¹⁴ seems at present the most plausible explanation. However, in the absence of detectable pathology such abnormal conduction in turn implies the presence of some factor affecting auricular metabolism which should be common to all cases, and the nature of which is as yet only vaguely conceived. That such a factor is not necessarily permanent is obvious from the existence of the paroxysmal types of fibrillation. That it must be persistently acting, and has not merely to initiate the arrhythmia, is apparent to all who are familiar with the extreme difficulty of producing persistent fibrillation of the normal auricle in experimental animals.

TABLE 3.—SEX INCIDENCE IN AURICULAR FIBRILLATION.

Etiology.	No. of cases.		Per cent.	
	Males.	Females.	Males.	Females.
Rheumatic fever	72	50	59	41
Arteriosclerosis	57	30	65	35
Syphilis	22	1	96	4
Thyroid	3	6	33	67
Miscellaneous	10	2	83	17
Total	164	89	65	35

SEX. The sex incidence is of interest. It will be seen in Table 3 that our series includes 164 males (65 per cent) and 89 females (35 per cent), a preponderance of 30 per cent in favor of the males. These figures are almost identical with those of Semerau¹⁵ and not greatly at variance with those of Lewis.¹⁶ Cookson,¹⁷ however, has reported a ratio of at least 2 to 1 in favor of women. We are inclined to believe that auricular fibrillation really predominates significantly in the male, although the figures are undoubtedly modified by the preponderance of cardiovascular disease among

men. This greater incidence is possibly explainable on the basis that with the onset of cardiovascular disease there is a greater tendency for men to continue with their work to the extent of overexertion than for women, who, in general, have more leisure for therapeutic rest.

Prognosis. Some of the most helpful facts to be learned from a statistical study of cardiovascular cases are those bearing on prognosis. Granted that to date our therapeutic measures can achieve only a limited prolongation of life in most types of cardiovascular

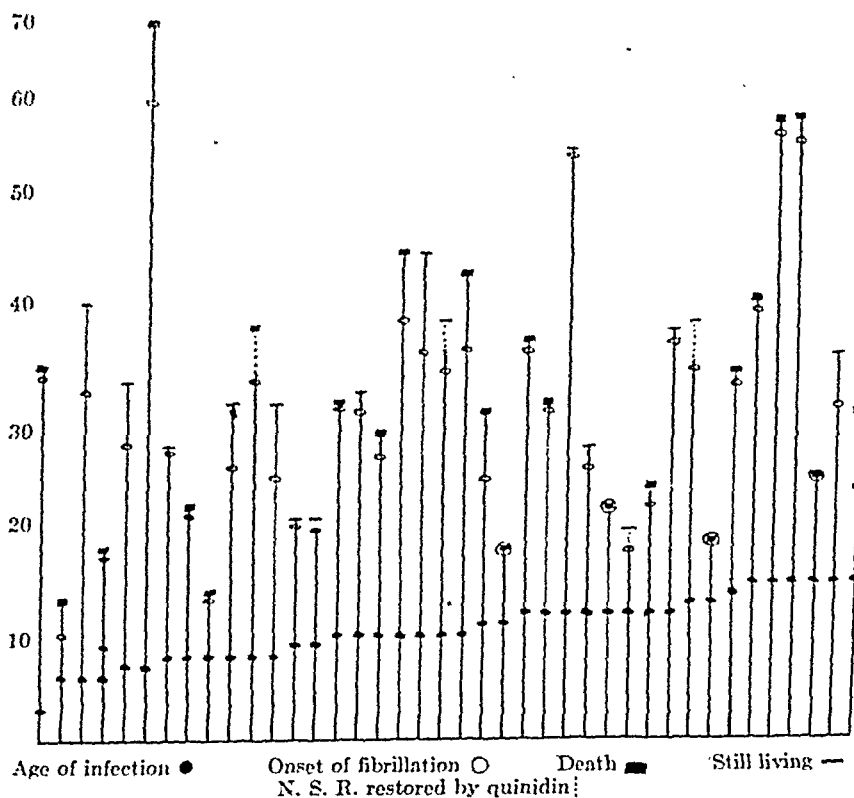


CHART I.—Age of infection; onset of fibrillation and death of rheumatic fibrillators.

disease, it becomes increasingly important that we be able to advise the patient as to the probable duration of his active life and the onset of his years of total disability, in order that he be able to arrange his economic and domestic affairs accordingly.

Charts I and II indicate the ages of infection, fibrillation and death of our rheumatic patients. Of the 77 cases illustrated 51 (66 per cent) developed their etiologic infection before the age of 20 years; 37 (73 per cent) of their number began to fibrillate between the ages of 20 and 40 years, and in this group the average duration of life was about 3 years thereafter; 7 (13 per cent) began to fibrillate

before 20 years, and their subsequent duration of life was less than 1 year. The remaining 7 (13 per cent) whose arrhythmia started after 40 years of age fibrillated for an average of 5 years.

It becomes apparent then that the age of onset of the fibrillation is of considerable importance in determining the life expectancy of the patient. Other things being equal, those hearts which are least damaged by a rheumatic infection should probably begin to

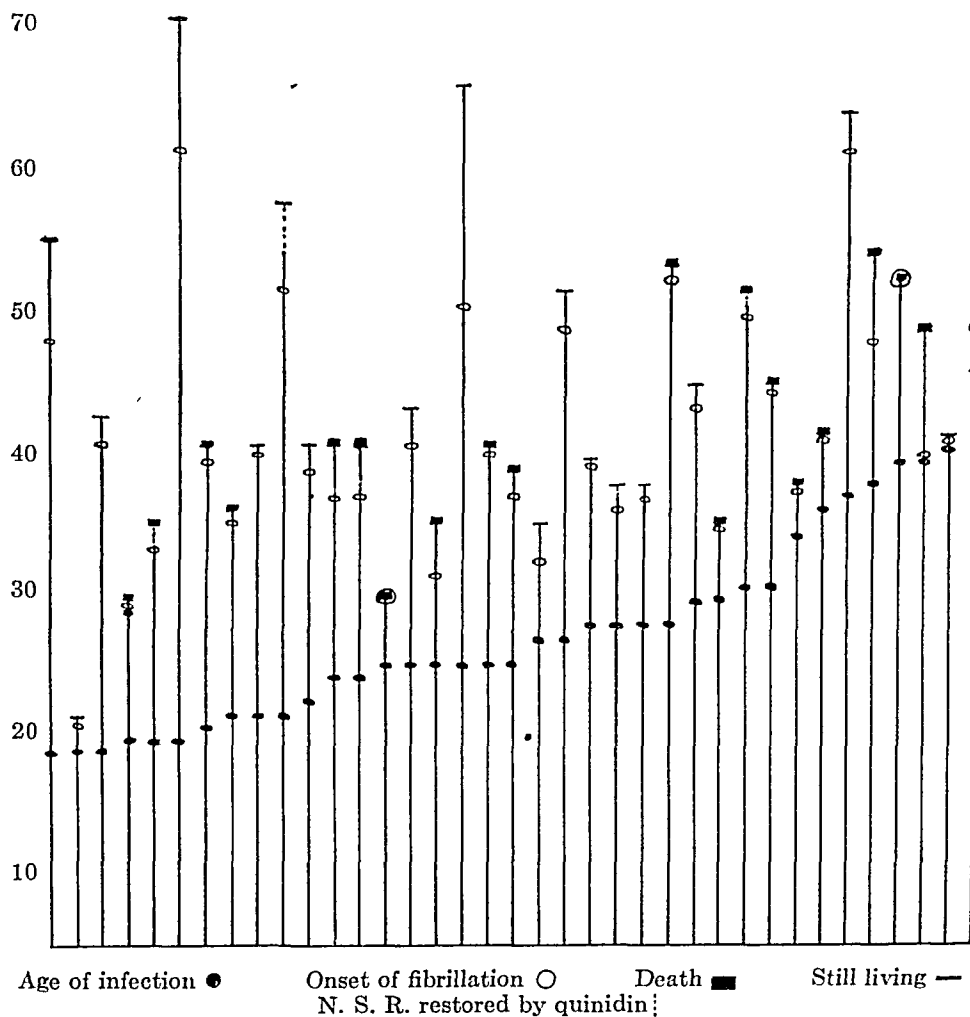


CHART II.—Age of infection; onset of fibrillation and death of rheumatic fibrillators.

fibrillate later and last longer thereafter than those in which the etiologic infection has been more destructive. Among the 26 (33 per cent) of the total group whose infection occurred after 20 years the average duration of life was about the same as the general average, that is, $2\frac{1}{2}$ to 3 years.

As to the comparative severity of the various forms of rheumatic infection, an indication will be found in Tables 4 and 5. A combination of arthritis and chorea is associated with the earliest

appearance of fibrillation and with a life expectancy of less than 1 year following its onset. Severe streptococcic tonsillitis is almost as ill-omened, while simple arthritis appears to give the best prognosis, with a duration of life of 2 to 3½ years after fibrillation and a maximum length of fibrillation in our experience of 16 years. Generally speaking, if we are justified in placing importance upon our results, of those patients with a history of rheumatic fever with resultant rheumatic cardiovascular damage before the age of 25 years, and who are going to develop auricular fibrillation, 86 per cent will develop this arrhythmia before the age of 40 years and 88 per cent will have died before the age of 53 years.

TABLE 4.—ETIOLOGY AND PROGRESS OF FIBRILLATORS NOW LIVING

Etiology.	No. of cases.	Age at etiological history.	Age at onset of cardiac symptoms.	Age at onset of fibrillation.	Age at onset of congestive failure.	Duration of fibrillation, years.	Maximum life after onset of fibrillation, years.
Rheumatic:							
Arthritis	32	18	34	41	37	3½	16
Chorea	1	8	28	28	28	2	2
Chorea and arthritis	2	11, 10	26	29	..	2	2
Tonsillitis	10	..	31	35	27	3	8
No history	12	..	34	38	39	2	3½
Arteriosclerosis	47	..	58	60	62	2½	8
Syphilis	9	36	53	55	61	2	3
Thyroid	5	39	40	42	51	2	3
Unknown	12	..	41	45	40	3½	11

TABLE 5.—ETIOLOGY, PROGRESS AND TERMINATION OF DECEASED FIBRILLATORS.

Etiology.	No. of cases.	Age at etiological history.	Age at onset of cardiac symptoms.	Age at onset of fibrillation.	Age at onset of congestive failure.	Age at death.	Duration of fibrillation, years.	Maximum life after onset of fibrillation, years.
Rheumatic:								
Arthritis	41	18	30	36	36	38	2	6
Chorea	2	8	30	35	36	38	2	4
Chorea and arthritis	3	11-18	21	27	27	28	1	1
Tonsillitis	7	..	29	30	30	31	1½	5
No history	13	..	34	38	40	41	3	6
Arteriosclerosis	42	..	57	58	60	63	3	11
Syphilis	14	30	50	52	52	54	2	7
Thyroid	4	24	32	44	45	46	2	3
Unknown	6	..	45	49	46	51	2	4

The arteriosclerotic type presents a rather different picture. Here the onset of fibrillation is frequently the first manifestation of heart disease, and with few exceptions occurs at a later date than

in the rheumatic group. Of our 88 patients with arteriosclerotic or "nonrheumatic" cardiovascular disease who developed auricular fibrillation none developed this arrhythmia before the age of 40 years and 72 per cent after the age of 53 years.

Much dissention exists as to which category offers the better prognosis of life expectancy, Coffen,¹⁸ Cowan and Ritchie¹⁹ and Jones²⁰ favoring the rheumatic type, while Clerc and Stieffel²¹ and Cookson²² find a better prognosis in the arteriosclerotics. Our own figures show a negligible difference, both groups averaging $2\frac{1}{2}$ years among those now deceased and $3\frac{1}{2}$ years among those still living. We feel in these two groups the comparative prognosis of life after fibrillation develops bears very little relation to etiology. The prognosis is best when fibrillation starts between 25 and 65 years of age irrespective of etiology, our maximum duration of fibrillation being 16 years in the rheumatic group and 14 years in the sclerotic group. Above and below these ages, however, the life expectancy is very short. Examination of Charts I and II, on the other hand, will point out a fact which must not be lost sight of in accepting the evidence of any statistics, namely, that a very definite group of patients die promptly after the onset of fibrillation and that these are balanced by an equal number who live far past the average life expectancy, irrespective of etiology or age of onset. This error will appear in even the largest series of cases, and for this smaller group the average prognosis must be modified by the judgment of the physician. It must be constantly borne in mind that the auricular fibrillation itself is apparently of very slight importance in determining the functional efficiency or duration of life of the patient compared to the severity of the myocardial damage. And, conversely, the extent of the myocardial damage beyond a certain degree is in no way indicated by the presence or absence of fibrillation. The residual myocardial reserve is the all-important factor.

The third group, those of miscellaneous or unknown etiology, are of comparatively indefinite characteristics. In thyrotoxicosis we have found that the majority of cases return spontaneously to normal sinus rhythm after partial thyroidectomy. The infrequency of fibrillation in cardiovascular lues, on the other hand, marks its onset as a bad prognostic omen. One of our cases has lived 7 years, but the average duration of life after fibrillation is only 2 years, which is the shortest of these groups. Finally, 11 cases (4.5 per cent) of our total series have had no apparent etiologic nor clinically demonstrable cause for their auricular fibrillation. Their average duration of life was 2 to $3\frac{1}{2}$ years. The average age of onset of fibrillation was 46 years as compared with 38 years for the rheumatics and 59 for the sclerotics.

Chart III presents graphically the duration of fibrillation in all our cases, irrespective of etiology, and will be referred to later

apropos of quinidin therapy. It indicates well, however, the number of patients who die promptly after the onset of fibrillation.

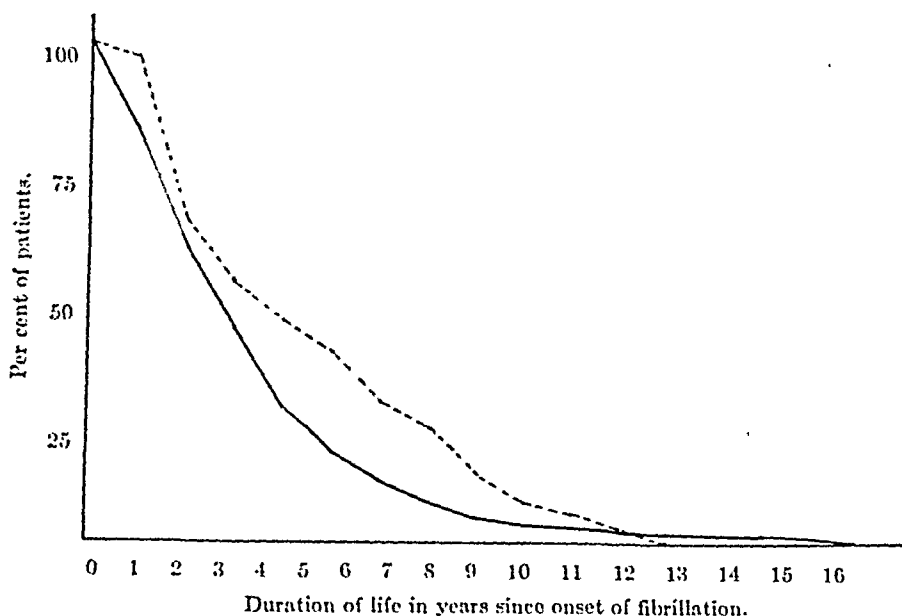


CHART III.—Comparative duration of life after onset of auricular fibrillation in cases successfully treated with quinidin and cases either unsuccessfully treated or untreated with quinidin.

———— Patients without quinidin or unsuccessfully treated with quinidin (219 cases).

- - - - - Patients who had a return of N. S. R. with quinidin (40 cases).

Treatment. The treatment of auricular fibrillation comprises an added factor not present in the case of a diseased cardiovascular system, but with a nonfibrillating heart. Primarily, one seeks, as with the average cardiac, to restore to as great a degree as possible the reserve of the myocardium. Secondarily, however, the physiologic deficiency of the arrhythmia must be overcome. This latter may be accomplished either by restoring the normal sinus rhythm or by eliminating the pulse deficit. The therapeutic procedures involved in effecting the former by means of quinidin sulphate and the latter by digitalization need not be discussed here. Both are now standardized routine in all clinics and our own methods have been described by us in a previous paper.²³

As to the results with quinidin, Wolff and White²⁴ have reported the successful restoration of sinus rhythm in 65 per cent of their series of 177 cases. This is about the average optimum. In our own series of 66 cases quinidin was effective in restoring the normal sinus rhythm in 40 patients (66 per cent). In a previous paper we reported our enthusiasm at these results. Since then, however, having followed these cases in the *interim*, amounting in some to

a period of over 7 years, our views have become less sanguine. These are mostly well-selected cases with the most favorable prognoses and with a minimum of determinable myocardial damage. Practically none of these cases developed congestive circulatory failure to any marked degree, in spite of the onset of auricular fibrillation. Nevertheless their average duration of life following the onset of auricular fibrillation was only slightly over a year longer than that of the patients who were considered unsatisfactory for quinidin therapy and exactly the same as that of the patients who had received quinidin but without the restoration of normal sinus rhythm. Surprising as these observations may be, they are quite in accord with the conclusions of Wolff and White,²⁵ that "there is no definite evidence that it (quinidin) prolongs life or reduces mortality."

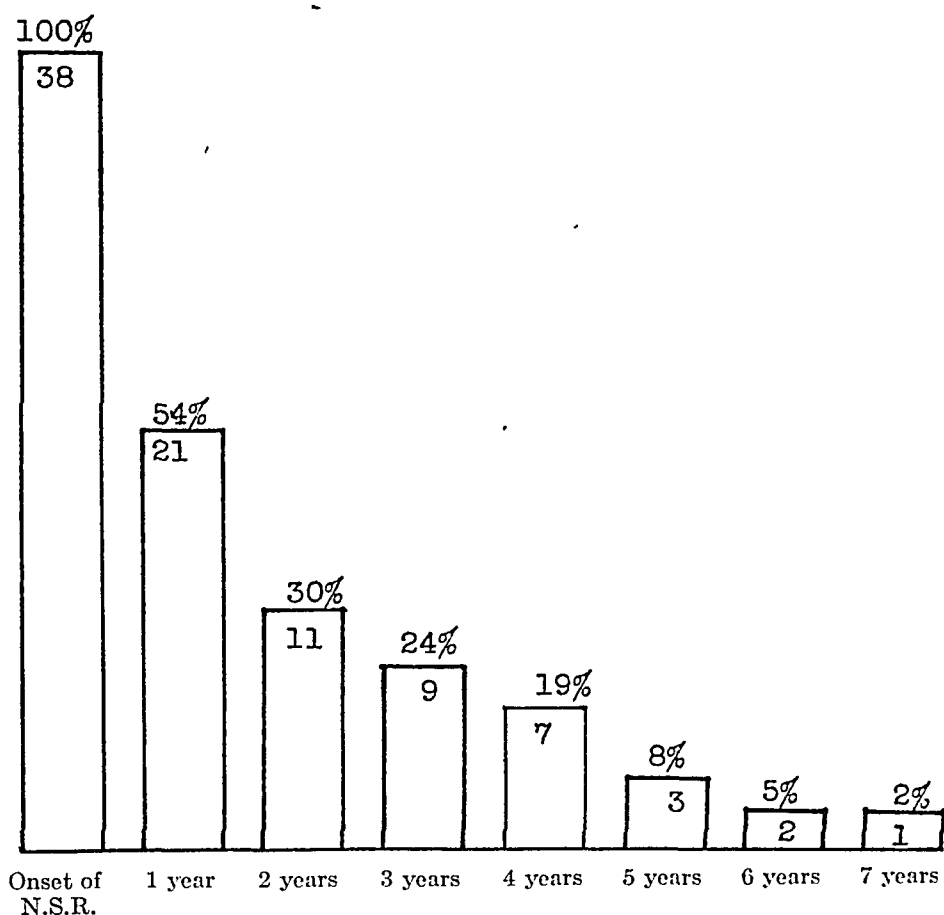


CHART IV.—Duration of normal sinus rhythm restored in 38 of 62 cases of chronic auricular fibrillation to whom quinidin sulphate was administered.

The average duration of sinus rhythm in our successful quinidin patients was $1\frac{1}{2}$ years, as indicated by Chart IV. In about one-half of the series it lasted less than 1 year; 1 out of every 4 lasted through

2 years; 1 out of 5 lasted through 3 years; 1 out of 20 lasted through 5 years. One case of the entire series preserved his normal sinus rhythm for 7 years and has just had a return to fibrillation. Marvin and White,²⁶ however, report somewhat better results, in that 30 per cent of their cases have continued with normal sinus rhythm for 6 to 7 years.

Obviously it is only in the cases where normal sinus rhythm is restored for a substantial length of time that quinidin may be said to be of definite value. On the other hand, we have found that the majority of our patients with restored sinus rhythm were no less "heart conscious" than during the period of their fibrillation under effective digitalis therapy. They were usually in a state of apprehension of the moment when fibrillation would return and thus necessitating the comparatively severe therapeutic régime of a second attempt to restore sinus rhythm.

In terms of the physiology of the circulation it is really very questionable whether the arrhythmia causes nearly as much circulatory embarrassment as one might *a priori* anticipate. Lewis²⁷ has shown that with the onset of fibrillation produced experimentally in laboratory animals there is an immediate fall in blood pressure, followed, after a brief interval, by a return to within the normal range. Clinically, such is unquestionably the case when the rate of the fibrillating heart is normal and there is no pulse deficit. Such a status is achieved in most cases by digitalis therapy. We feel, therefore that quinidin is indicated only in a comparatively few carefully selected cases of younger individuals in whom there is apparently no other evidence of cardiovascular abnormality except the auricular fibrillation.

As to the incidence of sudden death following the use of quinidin, only 2 cases of such an accident occurred in our series. In neither of these instances do we feel that quinidin could be fairly indicted as similar occurrences of equal frequency have been reported among cases to whom no quinidin had been given and who had comparable cardiovascular pathology. Our feeling in this regard is in concurrence with Viko, Marvin and White,²⁸ Parkinson and Campbell²⁹ and Lewis,³⁰ who believe that the incidence of embolism and sudden death among patients carefully treated with quinidin is no greater than in a control digitalis group.

Summary. In a series of 253 cases of chronic auricular fibrillation we have endeavored to determine: (1) The principal etiologic factors; (2) the prognosis on a basis of etiology, age and extent of cardiac damage; (3) the comparative merits of treatment with digitalis and quinidin.

Throughout the series no common etiologic factors have become apparent. It is our impression that the presence of auricular fibrillation does not necessarily imply a worse prognosis than in the non-fibrillating heart with an equal amount of cardiovascular damage.

In our series the average age of onset of auricular fibrillation due to rheumatic cardiovascular damage in 39 years. The prognosis is very poor in such patients developing fibrillation before the age of 25 years. Of our 65 patients with manifestations of rheumatic cardiovascular disease before the age of 25, 86 per cent had developed auricular fibrillation before the age of 40 years and 88 per cent had died before the age of 53 years.

The average age of onset of auricular fibrillation in our arteriosclerotic ("nonrheumatic") group is about 59 years. Of our 88 cases none had begun to fibrillate before the age of 40 years and 72 per cent developed auricular fibrillation after the age of 53 years.

Fibrillation associated with thyrotoxicosis will usually terminate spontaneously following partial thyroidectomy, and if not, almost invariably will respond promptly to quinidin therapy after such an operation.

Syphilitic cardiovascular disease is comparatively rarely associated with auricular fibrillation.

In the treatment of patients with auricular fibrillation digitalis usually proves most satisfactory. It is only in the exceptional case that a restoration to normal sinus rhythm by quinidin sulphate is of more apparent value to the patient than the establishment of a daily maintenance dose of digitalis.

Although there appears to be little danger of accident from the use of quinidin sulphate in properly selected cases of auricular fibrillation, yet we feel this drug should only be used in those few cases of younger individuals with slight or no demonstrable cardiovascular abnormality except the arrhythmia, or in thyrotoxic patients following partial thyroidectomy without a spontaneous return to normal sinus rhythm.

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SUBACUTE BACTERIAL ENDOCARDITIS, WITH SPECIAL REFERENCE TO THE VALVULAR LESIONS AND PREVIOUS HISTORY.

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THERE has been much written and taught concerning subacute bacterial endocarditis in recent years and at present the diagnosis in most cases is not difficult. Certainly the younger practitioners and medical students are quite familiar with its commoner manifestations so that the diagnosis is ordinarily suspected in general practice, even though the absolute decision may require laboratory or more expert aid. An aspect of this disease which has not been particularly investigated is the relation between the past history and the previous heart findings to the subsequent development of subacute bacterial endocarditis. It has occurred to us that certain individuals are more liable, and others are less liable to develop this condition. The study here reported has been concerned mostly with this phase of the question, although other clinical considerations have been investigated that seemed to be of interest.

Some reference already has been made to incompatibilities between certain findings in the heart and this disease. For example Libman and associates^{1,2} called attention to the great rarity of auricular fibrillation in subacute bacterial endocarditis. Libman² also noted the infrequency of this disease in patients "suffering

from marked so-called decompensation." Levine³ noted that subacute bacterial endocarditis seldom develops in patients with well marked mitral stenosis and believed it was more common in patients who had a well compensated mitral or aortic insufficiency, despite the fact that mitral stenosis is the most common rheumatic valve lesion. At this time no proof was offered for this opinion, but recently Sprague⁴ investigated the size of the mitral valve in 20 autopsied cases of subacute bacterial endocarditis, and concluded that well-marked constriction of the mitral valve was uncommon.

Previous reviews of this subject have emphasized the great frequency with which the mitral valve is involved in subacute bacterial endocarditis. Thayer's⁵ figures for 60 cases were 80 per cent and 58 per cent for mitral and aortic involvement respectively. Clawson⁶ in 72 cases found the mitral valve affected in 76 per cent, the aortic in 47 per cent. Out of 146 cases studied, Blumer⁷ found the mitral valve alone involved in 40 per cent, the aortic alone in but 11 per cent. On the other hand, several observers^{8, 9, 11} were of the opinion that the aortic valve was more frequently involved. A few years ago when the opinion was expressed in conversations with some American physicians who have been particularly identified with this subject, that subacute bacterial endocarditis was comparatively rarely seen in patients with mitral stenosis, this idea was thought to be untrue. Confusion we believe has resulted because it was inferred from the great frequency of mitral valve involvement in subacute bacterial endocarditis that mitral stenosis was the valvular lesion present in these cases. The data presented here confirm our opinion that although the mitral valve is a common site for subacute bacterial endocarditis, mitral stenosis is rare.

A further feature that has interested us for some years has been the relationship between the previous general health of the patient, the degree of rheumatic infection, and the susceptibility to subacute bacterial endocarditis. It has been very striking that so many of these patients had been comparatively free from recurrent rheumatic infections and had been able for years to carry on their usual activities satisfactorily just preceding the onset of the final illness. Contrariwise, it has also seemed that those patients who were much more sickly and had frequent recurrent bouts of rheumatism did not generally succumb to subacute bacterial endocarditis. An investigation in this regard was made of the cases reported below.

Material Analyzed in This Study. All of the cases of subacute bacterial endocarditis observed in the medical wards of the Peter Bent Brigham Hospital from 1913 to 1930 and those seen by one of us in private consultation practice during the past 11 years were analyzed. Only those cases were included in which a review of all of the clinical data made the diagnosis quite certain. There were 111 such cases in 30 of which postmortem examination was performed. There were 67 males and 44 females. The ages varied

from 12 to 64 years. A detailed discussion of the relation of age to this disease will be taken up below. In 95 cases blood cultures were obtained during life, and in 67 of these the cultures were positive. The other 28 showed negative blood cultures, although in 8 instances only one culture was taken during life. In 5 of the negative cases, positive results were obtained on culturing the blood at autopsy. Except for 2 cases that showed atypical organisms, *Streptococcus viridans* was the organism isolated in all the positive cases.

The Valvular Lesions in Subacute Bacterial Endocarditis. It is generally agreed that subacute bacterial endocarditis becomes engrafted on previously injured valves. Although this injury is most frequently the result of an antecedent rheumatic endocarditis, in a much smaller number of cases the defect in the endocardium is congenital in nature. Unlike pneumococcus and gonococcus endocarditis subacute bacterial endocarditis due to *Streptococcus viridans* rarely if ever develops in a previously undamaged heart. It is difficult to obtain the absolute proof of such a generalization because it would necessitate careful and repeated observation of the heart by the same observer both before and after the development of this disease. At times it is even difficult at autopsy to be certain that a previous valvulitis existed. There is some indirect evidence, however, that lends support to this view. In the first place, it is extremely rare to fail to find some sort of a murmur in cases of subacute bacterial endocarditis. All but 1 of the 111 cases in this review showed at least a systolic murmur. The one exception occurred in a woman who was first seen only 5 days before she died and the heart at this time was very rapid. There is reason to believe that a heart murmur was present at a previous time because a diagnosis of heart disease had been made 2 years before. The constancy of the finding of heart murmurs obtains even during the very early stages of the disease, although murmurs may change in character and new ones develop. Second, in an appreciable number of our cases it was definitely known that a heart murmur was present for many years before the development of subacute bacterial endocarditis. Finally, as a purely clinical experience we have never seen a patient showing no heart murmurs whatever who subsequently developed subacute bacterial endocarditis unless they had an intercurrent infection resulting in a heart murmur between the time of the first examination and the final illness. From the above evidence we are of the opinion that a previous injury to the endocardium, either acquired or congenital, is a prerequisite for the subsequent development of subacute bacterial endocarditis due to *Streptococcus viridans*. As a practical corollary, one can dismiss the diagnosis of subacute bacterial endocarditis in any doubtful case if no murmurs whatsoever are present. If there are exceptions to these general rules, they must be extremely rare.

The type of valvular disease present in the 111 cases in this study was analyzed from a clinical point of view. The 30 autopsied cases were also reviewed and these served as an important control on the interpretation of bedside findings. There were 23 instances in which a systolic murmur alone was heard over the precordium. This murmur was generally best heard at the apex and varied in intensity from moderate to very loud. We interpreted this as indicating mitral endocarditis with mitral insufficiency. The validity of this interpretation is borne out by the fact that in all 4 of the cases of this group in which an autopsy was done, the endocarditis was confined to the mitral valve and there was no mitral stenosis.

There were 66 patients that showed a systolic murmur at the apex and a systolic and aortic type of diastolic murmur at the base of the heart. These were all grouped as having aortic and mitral insufficiency. Twelve of them showed a sufficiently prominent diastolic murmur at the apex to suggest the possibility of mitral stenosis. It is well known that the interpretation of a diastolic murmur at the apex in the presence of aortic insufficiency is difficult, for it may be the same aortic diastolic murmur that is present at the base of the heart which is loud enough to be heard at the apex. Even if it is presystolic in time it may yet be the Austin Flint murmur without mitral stenosis. Not infrequently in this group of aortic cases competent observers incorrectly made a diagnosis of mitral stenosis on the basis of an apical presystolic murmur and thrill. In fact there were 5 instances in which a definite apical presystolic murmur was heard, 4 of which also had a presystolic thrill, that did not show mitral stenosis at postmortem examination. Moreover there were 2 cases in which the Roentgen ray finding of fullness in the region of the left auricle suggested mitral stenosis that was not subsequently confirmed at autopsy. It follows that in patients with subacute bacterial endocarditis who have aortic insufficiency, the additional diagnosis of mitral stenosis must be made with caution, even when there is a presystolic thrill at the apex of the heart.

The second major group of these 66 cases that was analyzed included those with evidence of aortic valvular disease which also showed a mitral systolic murmur. There were 54 of these, all of whom had aortic insufficiency and 10 of them had signs of aortic stenosis as well. We do not imply that such aortic cases with an apical systolic murmur necessarily had a mitral vegetative endocarditis, for many of them may well have had a mitral systolic murmur due to relative insufficiency resulting from the enlargement of the left ventricular cavity, which accompanies aortic disease. This is even true when the apical systolic murmur is loud. In fact of 21 cases that were examined at autopsy, 13 showed vegetative lesions on both aortic and mitral valve and 8 only on the aortic valve, despite the fact that they all showed a mitral systolic murmur.

It may be added that in no case showing aortic and mitral murmurs was the vegetative process confined to the mitral valve. In other words, with clinical signs of aortic involvement there were always vegetative lesions on the aortic valve. Conversely every case that showed vegetations on the aortic valve at autopsy had an aortic diastolic murmur during life.

There are three significant conclusions to be drawn from these observations. First, the presence of a systolic murmur alone indicates a lesion confined to the mitral valve. (One exception to this is the rare instance of aortic stenosis or congenital heart disease with a systolic murmur in which no diastolic murmur is heard.) Second, an aortic diastolic murmur which generally is accompanied by an apical systolic murmur always indicates involvement of the aortic valve with which there may or may not be a lesion of the mitral valve. Finally, in the absence of an aortic diastolic murmur or definite signs of aortic stenosis, it can be predicted that the aortic valves will show no vegetations.

An important consideration in this study is the actual frequency of mitral stenosis in our cases of subacute bacterial endocarditis. (By mitral stenosis is meant a definite constriction of the orifice which during life produces the customary signs and at autopsy shows an appreciable narrowing of the valve.) This can be analyzed from either bedside or postmortem findings. The difficulties of the clinical diagnosis especially in the presence of aortic disease have been discussed above. But even where the disease is confined to the mitral valve it is no simple matter at times to decide whether the valve is actually stenosed or not. Occasionally the mitral orifice is constricted by a mass of vegetations engrafted on a valve which, although the site of previous injury, is not narrowed. Such conditions may well produce the customary physical signs of mitral stenosis, as occurred in one case in this series that came to autopsy. An analysis of all of our 111 cases showed that in 19 instances the physical signs were such that a diagnosis of questionable mitral stenosis was made. In 8 other instances the evidence was sufficient to warrant a *definite* clinical diagnosis of mitral stenosis. Of the 30 cases that came to postmortem examination 4 showed definite mitral stenosis. In many of the other cases studied at autopsy the mitral valve whether the site of vegetations or not, showed evidence of old rheumatic endocarditis with thickening of the edges of the valve and retraction but no mechanical stenosis. If all the questionable cases are included 24.3 per cent of the cases were diagnosed as having mitral stenosis but only 7.2 per cent were diagnosed as having definite mitral stenosis. The incidence of mitral stenosis in the cases examined at autopsy was 13.3 per cent. Considering the great frequency of mitral stenosis* as a definite finding in cases of

* During the period covered by this study approximately 900 different cases of mitral stenosis were admitted to the Peter Bent Brigham Hospital or were seen by one of us in private practice.

rheumatic valvular disease its occurrence in this series judged by the data obtained either at the bedside or postmortem is quite rare.

The remainder of the cases that made up this series consisted of small heterogeneous groups, of which the most important was that with congenital heart disease. There were 5 such cases, 2 of which were examined postmortem. One of these was found to have vegetative endocarditis engrafted on a patent ductus arteriosus, with vegetations on the aortic and pulmonary valves both of which were bicuspid. In the other, vegetations developed on a bicuspid aortic valve. The importance of congenital abnormalities of the heart as a predisposing factor in the subsequent development of bacterial endocarditis has been emphasized by Lewis and Grant.¹¹ There were only 3 other cases that have not been discussed, 1 of which was of some interest. This was the only instance in which a definite diagnosis of aortic stenosis was made where no diastolic murmur could be heard. It therefore could not be included among those with aortic insufficiency. In only 1 of the 30 autopsies were vegetations found on the tricuspid valve.

Mention has been previously made concerning the differences of opinion as to the frequency with which various valves are involved in subacute endocarditis. Although most writers have felt that the mitral valve was the most common site for the development of vegetations, others have thought the aortic was more commonly involved. In this series of 30 cases that were examined postmortem, vegetations were found confined to the mitral valve in 8 instances, and to the aortic valve in 8 instances. In 13 cases both were involved, and in 1 case the aortic and tricuspid valves showed vegetations. The inference from this small series is that the aortic and mitral valves are affected with approximately equal frequency.

Does Organic Mitral Insufficiency Occur? An interesting and significant sidelight that developed in the course of this study concerns certain data that seem to indicate the existence of regurgitation without stenosis of the mitral valve during life. There has been much written about this subject. Until a short while ago organic mitral regurgitation was a common clinical diagnosis. Mainly as a result of experiences in the Great War, when large numbers of young men were found to have a slight systolic murmur but no organic heart disease, the pendulum has swung to the extreme opposite position. There is at present a tendency to the view that regurgitation without stenosis of the mitral valve does not exist. With this there has been a growing belief that apical systolic murmurs in the absence of other signs of heart disease are of no significance whatever. In discussing whether mitral regurgitation exists and explaining why this diagnosis is incorrectly made so frequently, Cabot¹² states that "physicians diagnose mitral regurgitation when they hear loud apical systolic murmurs which are extremely common in all sorts of noncardiac disease as well as in health." (P. 290.)

Later (p. 291) he adds that "systolic murmurs without other signs of cardiac disease are of no importance as evidence of valve lesions." Speaking about regurgitation without stenosis of the mitral valve he continues (p. 292) "perhaps in ulcerative endocarditis such a state of things may occasionally exist." In conclusion he states "a diagnosis of mitral regurgitation without stenosis is never justified." (P. 296.) Fully aware of the fact that systolic murmurs occur in a variety of conditions both in which the heart is not diseased at all or in which the valves in particular are normal, we do believe that there is a distinct group of cases showing a moderately loud or a loud apical systolic murmur where this sign is the main evidence of an organic mitral lesion producing mitral regurgitation without stenosis. Such patients are often entirely free from all symptoms and frequently have been refused life insurance because of this murmur. The heart need not be appreciably enlarged and in fact complete examination may be otherwise negative. Commonly a past history or family history of rheumatic fever may be elicited or some other evidences of the rheumatic state uncovered, such as recurrent nosebleeds and the like. At this stage these patients rarely die. Many of them eventually develop mitral stenosis and later die of congestive heart failure. On postmortem examination, therefore those patients, in whom the progress of the disease was not prematurely interrupted and who died of congestive heart failure, will show mitral stenosis. Subacute bacterial endocarditis, however, is just such an event that prematurely cuts short the development of the progressing valve lesion long before there would have occurred congestive heart failure. This enables us to see the mitral valve at autopsy at a stage of incompetency without stenosis. In this series of 30 postmortem examinations there were 6 instances in which the vegetative endocarditis was limited to the mitral valve and the lesion, though producing an insufficiency as evidenced by a mitral systolic murmur in life and pathologic changes at autopsy, did not show mitral stenosis. There were numerous other instances in which only a systolic murmur was known to be present for years antedating the terminal illness. Many of these we regard as having had organic mitral insufficiency with structural changes in the valve, as it is known that subacute bacterial endocarditis almost never develops on previously normal valves. We, therefore, feel that one is justified in making the diagnosis of organic mitral regurgitation in patients showing a moderately loud apical systolic murmur in whom other causes such as hypertension, anemia, and the like are lacking, especially where a past history or family history identify the individual as being rheumatic.

Previous History of Infections and General State of Health. It is generally recognized that some history of rheumatic infection is frequently obtained in cases with subacute bacterial endocarditis.

We became interested in analyzing this in greater detail, especially determining the more exact character of this antecedent illness. In this series of 111 cases there were 42 with a history of rheumatic fever alone. There were 3 that only had chorea, and 6 that had both chorea and rheumatic fever. It is striking that chorea, of itself, is so rarely found in the past history of these patients. In 100 cases of rheumatic heart disease, Coombs¹³ noted 18 instances in which a history of chorea was the only other rheumatic manifestation. He found 30 instances in which chorea was associated with other rheumatic features such as arthritis or nodes. It follows that in cases of subacute bacterial endocarditis a past history of chorea is obtained much less frequently than occurs with rheumatic heart disease in general. This is in keeping with the above-mentioned conception that mitral stenosis is rarely the seat of subacute bacterial endocarditis, for chorea has a peculiar predilection for the mitral valve producing eventually stenosis of the valve. Strong¹⁴ found that in 45 valvular cases due to chorea the mitral valve was involved in 44 instances, the aortic in 1, and in 4 both were involved.

There were 15 patients who gave a past history of scarlet fever, 3 of whom also had rheumatic fever and 1 had chorea. Scarlet fever seems to be somewhat allied to rheumatic fever as an etiologic factor in producing valvular disease. A careful analysis of the history of patients in whom scarlet fever was supposed to have initiated valvular disease will frequently disclose the fact that in the wake of the scarlet fever there have been vague pains in the limbs. May this not be an associated rheumatic infection? Scarlet fever was the only other specific disease that was commonly found in the past history of these patients.

The question arises whether syphilitic disease of the aortic valves ever serves as the locus for subacute bacterial endocarditis. In this series there were 9 instances with a positive Wassermann reaction. An analysis of these 9 cases discloses that 6 of them also had a previous history of rheumatic fever and another had scarlet fever. In 4 the valvular lesion was mitral insufficiency and therefore syphilitic disease of the valves need not be considered, especially as 3 of these had had rheumatic fever. Likewise another one of these with a positive Wassermann had aortic stenosis which we feel quite sure was not syphilitic, as he previously had had rheumatism. This leaves 4 cases with aortic insufficiency 2 of which had rheumatic fever and 1 scarlet fever. The remaining 1 had Argyll-Robertson pupils and no history indicating a rheumatic infection. This serves as the single instance in the entire series that one might reasonably regard as having had subacute bacterial endocarditis engrafted on luetic aortic insufficiency. One may conclude, as does Thayer⁵ that syphilis as a predisposing agent in streptococcus endocarditis is extremely rare.

Of the remaining cases in this series, there were 6 in which the

data concerning the past history were insufficient. There were 2 patients who had no other previous infection except pneumonia and 2 others in which a questionable history of rheumatic fever was elicited. Finally, in 39 cases no history of any significant previous infection could be obtained. We are of the opinion that if more were known about the past history and family history of such negative cases, many of them would have been identified as being rheumatic.

Mention was made earlier in this discussion that many of these patients were singularly free from recurrent rheumatism before developing subacute bacterial endocarditis. Of the 42 cases that had rheumatic fever as the sole predisposing cause, 28 had only one attack, and thereafter were free of rheumatism. The average interval that elapsed between the rheumatic fever and the development of subacute bacterial endocarditis was 17.5 years. This interval varied a great deal, the extremes being 6 months and 44 years. There were 7 others who had 2 bouts of rheumatism. The remaining 7 cases had three or more attacks. It is very difficult to compare these figures statistically with the type of rheumatism that occurs in the larger group of rheumatic heart disease. It is certainly striking, however, that a smouldering rheumatic infection continuing with varying intensity for years that we so commonly see in our heart clinic, was almost never found in the past history of these patients. They generally had one, sometimes two discrete attacks and then there followed a period of freedom and wellbeing until the onset of the bacterial type of endocarditis.

Although there is a sequential relationship between rheumatic valvular disease and subacute bacterial endocarditis in the sense that the latter is generally engrafted on the former; from an entirely different point of view there is also a peculiar antagonism between the two diseases. It has seemed that those who clinically become immune to rheumatic fever are most apt to develop subacute bacterial endocarditis and contrariwise, those who continue with rheumatic manifestations are the least likely subjects. To this clinical conception which we have had for some years there has recently been given certain immunologic support. Whereas cases of rheumatic fever show a very high incidence of positive skin reactions to streptococci or their derivatives (as high as 88 per cent) similarly positive reactions are very rarely found in subacute bacterial endocarditis. Howell and Corrigan¹⁵ found no positive skin reactions to filtrates of streptococci in 7 patients with subacute bacterial endocarditis. Swift¹⁶ had 2 cases with negative reactions, and of 4 of the patients in this present series tested by Derick and Fulton¹⁷ only 1 gave a mildly positive reaction. Furthermore Swift¹⁶ never found a high degree of serum immunity in rheumatic fever patients against the strains of streptococci occasionally recovered from them, whereas patients with subacute bacterial endocarditis are known frequently to have serum of high agglutinating

titer to *Streptococcus viridans*.^{16,18} Finally, Wright¹⁹ was able to produce bacterial endocarditis much more regularly if the animals were previously immunized.

It may be permissible to draw a somewhat speculative and theoretical inference from the above immunologic considerations. There is an apparent incompatibility between the state of susceptibility to rheumatic fever and the simultaneous susceptibility to subacute bacterial endocarditis. It has been shown above that mitral stenosis rarely forms the background for bacterial endocarditis. May one not infer that the progressive development of mitral stenosis is a local evidence of a continued allergic condition in the heart and that the rheumatic state may be persisting even in the absence of limb pains or fever? If this were true it would help to explain the rarity of subacute bacterial endocarditis in patients with mitral stenosis on the assumption that such patients have not developed the immunity requisite for subacute bacterial endocarditis. Furthermore, it may be inferred that any measure which renders a patient immune to rheumatic infections and does away with the allergic state during the early part of the disease may actually serve to prevent the subsequent development of mitral stenosis.

The general health of these cases previous to the development of subacute bacterial endocarditis was analyzed, particularly from the point of view of circulatory efficiency. Libman² was interested in a similar aspect of this question and stated that "it is noteworthy that the infection occurred mostly in persons who did not know they had a valve lesion; or knew it but had no symptoms, or slight or moderate symptoms only." Only rough estimates could be made but some general opinion was obtained concerning the ability of our patients to do heavy or light work, whether they had had much dyspnea, and especially whether they had had much heart failure. They were divided into three groups. The first included those who had *excellent* cardiac function. They had no symptoms referable to the heart, and many were even performing very vigorous work. The second were regarded as being in *good* condition, *i.e.*, they had slight dyspnea and palpitation at times but were able to work. The third group we considered as in *fair* health. These had more definite dyspnea but were ambulatory and never had had congestive heart failure. With this arbitrary subdivision it was found that in 76 the circulation was in excellent condition, in 17 it was good, and in 10 it was fair. There were 8 cases in which these data were not available. There were no instances in which congestive heart failure was known to have occurred prior to the development of subacute bacterial endocarditis. It is striking that approximately three-fourths of the patients were in excellent condition and that an additional 15 per cent were regarded as in good condition. A common experience was to learn that the patient was vigorous, able to

do hard physical work, or to play active games like tennis. In general it seemed that the very well compensated cardiac patients with aortic or mitral insufficiency were the ones most prone to develop subacute bacterial endocarditis.

In this connection, a study was made of the previous existence of heart disease, and especially of a heart murmur. Although many of these patients had felt well for long periods of time, they were aware of the fact that someone had heard a murmur in their hearts many years before or they had been told they had heart disease at some previous time. It is more than likely that the diagnosis of "heart disease" in such cases had been made on the presence of murmurs because these cases include practically no instances of angina pectoris, auricular fibrillation or congestive heart failure and only rare instances of hypertension. In 60 of our cases definite information could be obtained concerning the presence of a previous heart murmur or of "heart disease." The average length of time elapsing between the patient's first knowledge of this and the development of subacute bacterial endocarditis was 12.3 years. The shortest interval was 1 year and the longest 45 years. We have no doubt that if we could have examined or questioned all these patients carefully before their final illness, most if not all of them would have shown evidence of valvular disease.

AGE AND SEX. When the question of age and sex was analyzed in detail, there appeared certain curious relationships. Of the entire series of 111 cases, there were 67 males and 44 females, a proportion of 3 to 2. This corresponds exactly to the proportion found by Blumer.⁷ In a study of 762 cases of mitral stenosis²⁰ the females predominated in a proportion of 2 to 1. The discrepancy in these 2 groups of cases again emphasizes the relative antagonism between mitral stenosis and subacute bacterial endocarditis. The average age of the males with subacute bacterial endocarditis was 35.7 years and of the females 26.9 years. It is rather peculiar that under the age of 20 there were 14 females and only 2 males. In all the succeeding decades (Table 1) the males predominated to an

TABLE 1.—AGE AT DEATH.

Years.	Males.	Females.	Total.
11 to 19	2	14	16
20 to 29	23	18	41
30 to 39	17	5	22
40 to 49	14	3	17
50 and over	11	4	15

increasing degree so that over 40 years of age there were 25 males and 7 females. This may be explained by the fact that with advancing years the females with rheumatic heart disease are more prone to develop mitral stenosis and are thereby less liable to subacute bacterial endocarditis.

On dividing the cases according to the type of valve lesion present similar differences in the age between the two sexes were found. Of 30 cases with mitral disease alone, there were 14 males with an average age of 37 and 16 females with an average age of 27. Of 42 cases in which the valve lesion was predominantly aortic insufficiency, there were 32 males (average age 35) and 10 females (average age 27). It is rather striking that in the mitral group the females actually predominate, whereas in the aortic group the males outnumber the females 3 to 1. Why it is that subacute bacterial endocarditis is so much more commonly seen in young girls than in young boys remains unexplained unless it is due to the greater prevalence of rheumatic fever in the female in the early years of life.²¹ This and other anomalies in age and sex distribution need further elucidation.

SIZE OF THE HEART. The average weight of the heart in 29 cases that were examined postmortem was 489 gm. These cases were subdivided into groups according to the site of localization of the vegetations. There were 7 with vegetations limited to the mitral valve. The average weight of the heart in this group was 396 gm. There were 8 in which the vegetations were limited to the aortic valve. The average weight here was 586 gm. There were 12 in which both valves were affected and they averaged 503 gm. The average heart weight of the 2 cases of congenital heart disease was 351 gm. As was expected those cases with only mitral involvement in general had comparatively small hearts, while those with aortic disease showed considerable enlargement.

Arrhythmias. It has been noted that irregularities of the heart in subacute bacterial endocarditis are rare.^{1,2} In this entire series auricular fibrillation was never found except in one instance as a terminal event. Electrocardiograms were taken in 62 out of 84 hospital patients. There were 2 cases that showed complete heart block and 2 additional ones in which *A-V* conduction was delayed. Premature beats were comparatively rare. Only 2 patients showed ventricular extra systoles and 1 showed both auricular and ventricular premature beats. To be sure, had the patients been examined more frequently, a few other transient arrhythmias might have been noted. The inference to be drawn is that the heart remains essentially regular in subacute bacterial endocarditis and furthermore that if a patient has auricular fibrillation it is extremely unlikely that he has or will ever develop subacute bacterial endocarditis.

BLOOD PRESSURE. Little attention has been paid to blood pressure findings in this disease. There were 92 patients in whom blood pressure readings were made. The average systolic pressure was 118 mm. and the average diastolic 52 mm. In order to obviate the effect that aortic insufficiency has on the blood pressure, an analysis was made of the readings of 25 cases in which the mitral

valve alone was involved. In this group the average systolic reading was 110 mm. and the average diastolic 64 mm. The figures differ somewhat from the average of the entire group, for the aortic cases on the whole would show a higher systolic and a lower diastolic pressure than the general average. There were only 4 cases with systolic readings over 150 mm. These were all instances of aortic insufficiency. The low average level of the blood pressure could not be accounted for by the age of the patients, for the average figures of the 15 cases over 50 years of age were systolic 119 mm. and diastolic 56 mm. It may be concluded that hypertension does not occur with subacute bacterial endocarditis except in a few instances in which the systolic pressure may be slightly elevated as a part of the phenomenon of aortic insufficiency. This may serve as an additional point in excluding the diagnosis of subacute bacterial endocarditis in any doubtful case.

PECULIAR ONSETS. A very extensive review of the mode of onset of this disease was published by Libman in 1918.² It is generally understood that the onset of subacute bacterial endocarditis is apt to be insidious. The patients, previously in good health, often begin to have grippe-like symptoms. There may be a sore throat during the early days of the illness but the more striking features are general malaise, weakness, anorexia, vague aches, headache, chills and sweats. During the early days or weeks they are often diagnosed as grip or "rheumatism" and sometimes the possibility of typhoid fever or tuberculosis is seriously considered.

What has particularly interested us in this aspect of the study have been unusual modes of onset that occurred in some of our patients. There were 4 instances in which the patients dated the onset of their symptoms to the extraction of teeth and in 2 others the symptoms seemed to be distinctly aggravated by this procedure. Although it is not absolutely certain that the disease had not already started before the teeth were extracted in the above 4 cases, it is likely that in some of them the operation precipitated the development of the subacute bacterial endocarditis, for they all had previously been feeling well. These experiences make one hesitate in advising the extraction of teeth in cases that are likely subjects for bacterial endocarditis.

Another group included those with a sudden onset of pain in the back, as the major complaint. Embolic manifestations producing sudden pain in the fingers, toes and limbs have been well recognized phenomena in this disease. A similar sudden pain in the side or back, generally unilateral, as an evidence of emboli to the kidney or spleen, has not been sufficiently emphasized as an early feature. There were 5 cases in this series in which sudden fairly severe pain in the back was the earliest distressing symptom. In 1 such case because the back pain was associated with gross hematuria and dysuria, the diagnosis of renal stone was incorrectly made for a

while. Careful questioning of this patient revealed that although he had been working until this pain occurred he had been losing weight and strength for more than a month. Similar information no doubt could be obtained in many cases antedating what was regarded as the major complaint. The importance of these observations is that subacute bacterial endocarditis must be thought of in patients complaining of sudden pain in the back if there are any other features like fever and a heart murmur that make this diagnosis at all possible.

Several other cases showed most unusual types of onset. In 2 the earliest symptoms were mental, with the development of definite psychoses. One of these was first seen by us in a psychopathic hospital. In another case the disease seemed to develop after a pelvic operation for bilateral salpingitis. A fourth had had a well compensated valve injury for years and had been doing strenuous work every day until he developed an apparently minor infection of the foot, as the result of stepping on a nail. From then on he ran a typical course of subacute bacterial endocarditis. No doubt with more extensive experience we will find other peculiarities in the mode of onset of this disease.

The Evaluation of a Systolic Murmur as an Aid in Diagnosis. It is not the purpose of this discussion to go into the details of the diagnosis of subacute bacterial endocarditis. Apart from the swinging temperature and the prodromal symptoms mentioned above, there are numerous findings occurring at one time or another that are sufficiently distinctive to enable one to make a presumptive diagnosis. These are enlargement of the spleen, clubbing of the fingers, sudden peculiar pains in the finger tips, showers of red blood cells in the urine, and characteristic rose-colored oval petechiæ, most commonly seen in the conjunctivæ. Of course finding streptococci in the blood stream by cultural methods serves as an important decisive confirmation of the diagnosis. However, there are instances in which none of the above findings occur for intervals of time, and as happened in several instances in this series, the first clue to the diagnosis arose from the proper evaluation of a systolic murmur. Because such a murmur is so frequently regarded as insignificant, little attention is paid to it when the symptomatology suggests some noncardiac conditions. Particularly is this true when the patient is known to have had the murmur for years. On the other hand it is just this sort of a patient with a well compensated heart showing a murmur for years who should always be suspected of having subacute bacterial endocarditis if he develops fever and vague or unexplained symptoms. As an illustration one of our cases was a woman, aged 55 years, who complained of general fatigue of 2 months' duration. During this time she had lost 18 pounds in weight, had had occasional headaches, a slight cough and complained of vague pains in the abdomen and left shoulder. There was a history of rheumatic

fever in childhood. Physical examination was entirely negative except for slight fever and a moderately loud systolic murmur. A presumptive diagnosis of subacute bacterial endocarditis was made which was confirmed by the subsequent development of typical petechiae and the finding of *Streptococcus viridans* in the blood stream. Another example was the patient cited above who came into the hospital with the diagnosis of renal stone, because of sudden pain in the left loin, dysuria and gross hematuria. Physical examination was essentially negative except for a loud apical systolic murmur. In fact at the time we saw him there was no fever. Because the systolic murmur remained unexplained on the basis of the diagnosis of renal stone, we questioned him more carefully and elicited the other vague symptoms that had preceded the attack of pain by a month or two. In both of these instances, as well as in others not detailed, it was the systolic murmur which first focussed our attention on the correct diagnosis.

TREATMENT. There is hardly a disease in which a greater variety of treatments has been tried than subacute bacterial endocarditis. Most observers are in accord with the belief that specific therapy is valueless. A few, however, feel that injections of sodium cacodylate have caused recovery. In our experience all the various therapeutic procedures employed have proved fruitless. We wish to record several instances in which novel methods of therapy were tried which also were ineffective. The general purpose of these procedures was the attempt to alter the immunologic state of the patients in some such way as occurs in the thermal treatment for general paresis or the nonspecific protein therapy in chronic arthritis. Two of our cases were deliberately given rat-bite fever. One other was injected with blood from a patient suffering from malaria. This case, however, did not develop malaria. A Bier operation²² was performed on a fourth patient. This consisted of cauterizing a large area under the left breast. This patient and 3 others were also given 1 or more subcutaneous injections of turpentine for the purpose of producing a sterile abscess. Although in one of these latter cases, the temperature promptly fell to normal and remained so for more than a month, no real benefit was derived from any of these methods. (Two other cases, not included in this series were given typhoid vaccine intravenously, in 1 of which at least a temporary disappearance of the fever was obtained.) Knowledge concerning the pathology and diagnosis of subacute bacterial endocarditis is extensive, but treatment except for hygienic care, is at present of no avail.

Summary. 1. A clinical study has been made of 111 cases of subacute bacterial endocarditis. Thirty of these were examined postmortem.

2. It is generally conceded that *Streptococcus viridans* endocarditis becomes engrafted on previously damaged valves. In spite

of the great frequency of mitral stenosis as a type of chronic valvular disease, it was found to be associated comparatively rarely with subacute bacterial endocarditis. Only 7 per cent of these cases showed definite clinical evidence of mitral stenosis and 13 per cent of those examined postmortem had mitral stenosis.

3. There were 23 instances of mitral insufficiency (showing a systolic murmur alone) and 66 of aortic and mitral insufficiency, 10 of which had signs of aortic stenosis as well. There were 5 with congenital abnormalities of the heart and the remainder consisted of small heterogeneous groups.

4. On postmortem examination vegetations on the valves were found as follows: mitral alone 8; aortic alone 8; both 13; aortic and tricuspid 1.

5. As a result of this study the following general rules may be formulated:

(a) If no murmur whatsoever is heard over the heart, one can practically dismiss the diagnosis of bacterial endocarditis.

(b) If only a systolic murmur is heard the vegetations will be found limited to the mitral valve and adjacent endocardium. (This excludes the rare cases of congenital heart disease.)

(c) If there is in addition to a systolic murmur a basal diastolic murmur, one may predict that there are vegetations on the aortic valve and that there may or may not be a similar lesion on the mitral valve.

6. A previous history of some definite rheumatic infection was obtained in 51 instances. Forty-two had rheumatic fever, 3 had chorea, and 6 had both. From an analysis of the degree and duration of rheumatic infection from which these patients suffered, they were found as a group to have been comparatively free from this type of infection for a considerable period of time preceding the development of subacute bacterial endocarditis. Twenty-eight of the 42 patients who had had rheumatic fever had had only a single attack. In these there was an average interval of 17.5 years before subacute bacterial endocarditis developed. It is our opinion, based on this clinical study and other immunologic data that the immunity to rheumatic infection developed in these patients, renders them more susceptible to subacute bacterial endocarditis.

7. A study of the past history of these patients from the point of view of ability to work and of circulatory efficiency, showed that the cardiac condition could be regarded as "excellent" in 76, "good" in 17, and "fair" in 10. There were no instances in which congestive heart failure was known to have occurred prior to the development of subacute bacterial endocarditis, though there was satisfactory evidence that in 60 cases heart murmurs had been present for a period of years. It is believed that had we been able to examine

these patients shortly before the development of subacute bacterial endocarditis most if not all of them would have shown a murmur.

8. The following are some of the other findings of interest in this study. The males outnumbered the females 3 to 2. The average age of the males (35.7) was 9 years greater than that of the females (26.9). The average heart weight in the autopsied cases was 489 gm. Significant arrhythmias were rarely found. Only 1 case showed auricular fibrillation and that as a terminal event. The average blood pressure in 92 patients on whom readings were obtained was 118 systolic and 52 diastolic. There were only 4 cases with a systolic pressure over 150 (all of whom had aortic insufficiency) indicating that hypertension is extremely rare in this form of heart disease. There were cases with very peculiar types of onset in which the evaluation of a systolic murmur was a most important clue to the diagnosis.

9. Several novel but ineffective methods of treatment were employed in some of these cases such as the production of rat-bite fever and malaria, typhoid vaccine intravenously, sterile turpentine abscesses, and cauterization of the breast (Bier method).

10. The patient who is most apt to develop subacute bacterial endocarditis is one who has had a mitral systolic or an aortic diastolic murmur for some years. If he gives a history of previous rheumatic infection, as happens in about half the cases, it is most likely to be of a single attack with unusual freedom from recurrences. He has been able to carry on essentially normal activities, has shown at no time any important irregularities of the heart or evidence of congestive heart failure, and has either a low or normal blood pressure.

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SARCOMA OF THE SPLEEN.

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PRIMARY sarcoma of the spleen is a rather uncommon disease. The frequency of its incidence may be shown by the fact that of 40,000 surgical cases at the Boston City Hospital only 2 cases of primary malignancy of the spleen were noted. Two cases of primary splenic malignancy are reported from the Mayo Clinic, and at the Massachusetts General Hospital the diagnosis of malignancy of the spleen has been made but four times and of these only 1 was proven by operation.

Smith and Rusk¹ have collected 104 cases of malignancy of the spleen and add 2 of their own. These 2 cases were endotheliomata, the growth arising from the sinuses of the organ. It is the opinion of these observers that lymphosarcoma is probably the commonest type and is usually part of a generalized process, appearing at the same time or later in other lymphatic structures. Since the paper by Smith and Rusk other cases have been added to the literature by T. Howard,² Ladreyt, Debrym, Beasley, Berman, Kohler, Adam, Eichenbusch and Krumbhaar,³ who added 4.

Krumbhaar states that the predominant symptom of malignancy of the spleen is splenomegaly. Pain in the left side or back and in the left shoulder, together with tenderness, is often present. Indigestion with flatulence and constipation is frequently noted. There may be a marked secondary anemia, and jaundice and anasarca are

occasionally seen, as is also fever and leukocytosis. The diagnosis is made on the rapidity of the growth and the exclusion of other causes of splenic enlargement.

Splenectomy is the only curative treatment and was successful in 21 of 39 cases collected by Smith and Rusk. Of the 18 deaths 7 resulted from the operation and 11 were due to recurrences.

The first case which we wish to report was operated upon by Dr. Guy P. Grigsby, and we thank him for the courtesy of permitting us to include his case in this report.

Case Reports. CASE 1.—C. R. J., white, aged 34 years, seen in August, 1927, gives the history of having had digestive upsets since the autumn of 1926, and in the past few weeks has become weaker and lost 15 pounds in weight. About 3 weeks ago he thought he had pleurisy and his chest was aspirated and 10 cc. of fluid removed. He has had no previous serious illness and his family history is entirely negative. The patient is undernourished; the mucous membranes show moderate pallor. The skin is atonic and clear of eruptions. The muscles are flaccid. The appearance is that of subnormal strength and energy, but not of physical distress. The tongue is furred, moist and rather pale. The eyes are negative. The capillary circulation is subnormal. The heart action is regular, rhythmic; the valve sounds are pure, except for a very faint systolic blow over the mitral area, transmitted toward the pulmonic area. The stomach is displaced toward the right on account of a mass, the gastric percussion note being elicited to the right of the midline, a distance of about 2 inches, with the greater curvature 2½ inches below the umbilicus. The liver is enlarged, palpable, smooth, of slightly increased firmness and measures 5 inches in right mammary line. The abdomen is asymmetric, the left side being larger than the right. The walls are thin, superficial veins distinct, with dilatation of the capillaries overlying the diaphragm to a moderate degree. On palpation, a mass is felt on the left side extending to nearly a level with the umbilicus and, reaching across the midline, continues under the free costal margin. A distinct notch can be felt on its lower border. It is fairly smooth, quite firm, slightly tender, fills the left flank and is palpable in the left lumbar region. Below the sixth and seventh costal margins the mass shows a prominence which is palpable and appears to be firmer than the remainder of the structure. There is a question about fluid in the pleural cavity. The chest is fairly well developed, respiratory movements rather shallow but regular. The right lung shows no definite pathology. The respiratory sounds are a bit harsh. The percussion note is unmodified and the vesicular murmur is heard over the entire lung. The left lung shows a similar condition except for some modification of the percussion note and râles over the base posteriorly. The left diaphragm is situated high on account of the mass in the abdomen and shows practically no range of respiration. The patient is mentally clear, with good memory. The speech is deliberate, but there are no defects. The reflexes are normal, superficial and deep. No ataxia or incoördination of gait is present. The hearing is normal.

Laboratory studies showed: Urinalysis, negative. The blood count on August 25, 1927, was: Red cells, 3,790,000; leukocytes, 6800; hemoglobin, 75 per cent; color index, 0.9; polymorphonuclears, 74 per cent; small lymphocytes, 15 per cent; large lymphocytes, 10 per cent; eosinophils, 1 per cent; basophils, 0. Morphology: Poikilocytosis, increase in blood platelets. August 29, 1927: Red cells, 4,970,000; leukocytes, 13,850; hemoglobin, 90 per cent; polymorphonuclears, 76 per cent; small lymphocytes, 20 per cent;

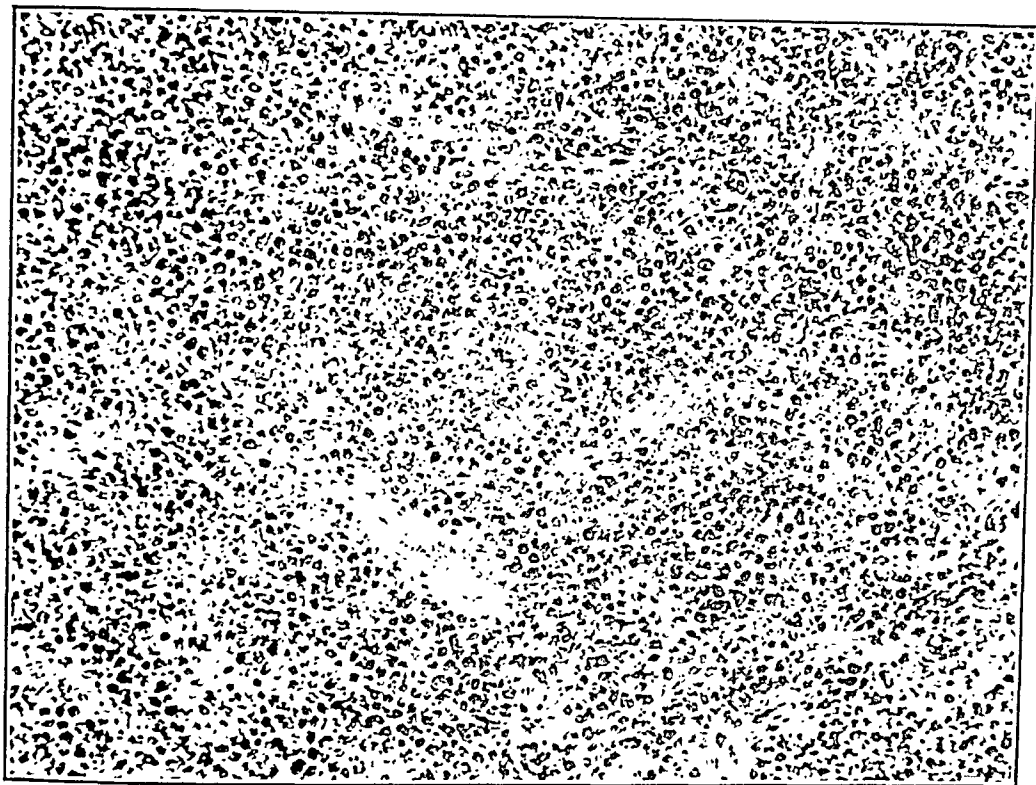


FIG. 1.—Case 1. Shows marked proliferation of lymphocytes with obliteration of normal splenic marking. Magnified 24 diameters.

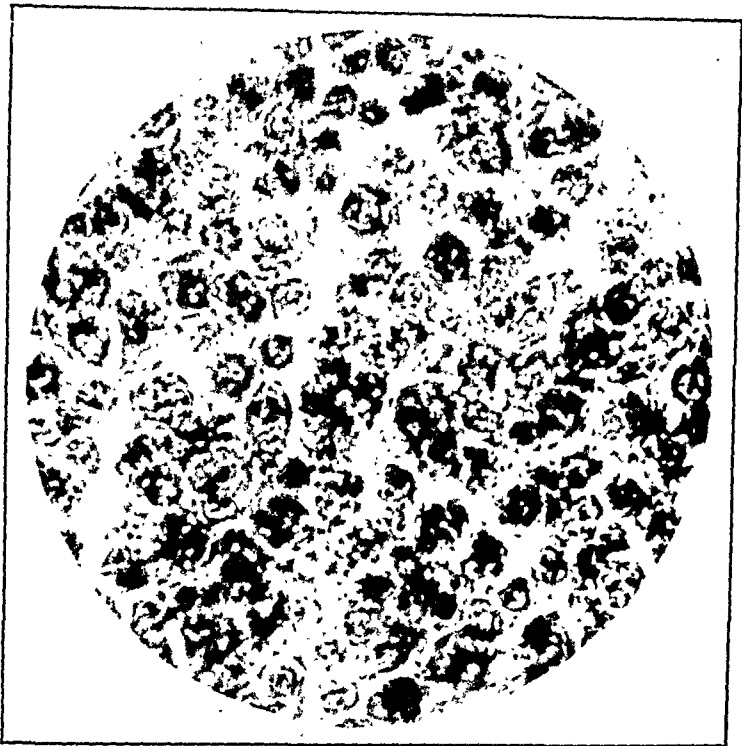


FIG. 2.—Case 1. Illustrates small amount of supportive tissue and marked rapidity of proliferation as shown by numerous mitotic figures. Magnified 900 diameters.

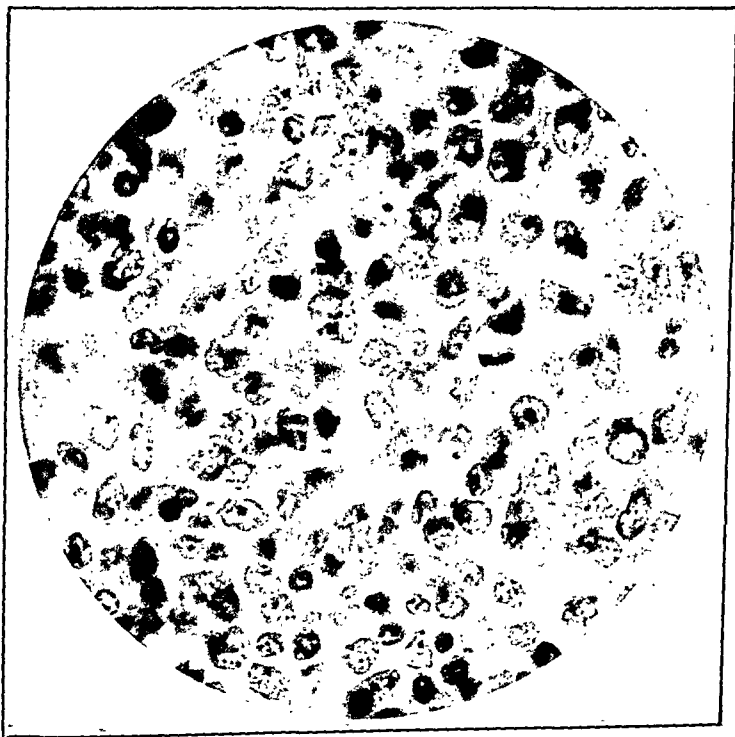


FIG. 3.—Case 2. Shows very little stroma. Marked proliferation as shown by numerous mitotic figures and appearance of diasters. Magnified 900 diameters.

eosinophils, 4 per cent. September 8, 1927: Leukocytes, 19,400; hemoglobin, 80 per cent; polymorphonuclears, 79 per cent; small lymphocytes, 15 per cent; large lymphocytes, 4 per cent; eosinophils, 3 per cent. Morphology: Increase in blood platelets.

The blood picture during the period of hospitalization changed rather rapidly and very definitely. The appearance of transitionals, lymphoblasts, eosinophilic leukocytes, large mononuclear leukocytes and an increasing anisocytosis being observed.

Gastric analysis showed slight retention but the chemical study revealed no abnormalities.

On December 5, 1927, after a transfusion of 500 cc. of citrated blood, the patient was operated upon by Dr. Grigsby. A right rectus incision was made and the abdomen opened, disclosing a large tumor that was densely adherent to all the surrounding structures, including liver, stomach, transverse colon and small intestine. The tumor had a nodular appearance, the upper portion being more or less solid and the middle being a large cyst. Enough of the adhesions were freed fully to expose the tumor and, as its appearance was suggestive of malignancy and it being so adherent to other important viscera, its removal was thought impossible. Palpation of the tumor caused considerable bleeding, particularly at the attachment of liver. A hot sponge placed on it controlled this and the abdomen was closed in the usual manner.

Following operation, he rapidly went into shock and died 24 hours later.

An hour after death the wound was reopened and further examination of the condition was made. The cyst was opened and found to obtain about 1 liter of rather thin grumous fluid that had the appearance of pus but was odorless and believed to be the result of a hemorrhage into the cyst. The adhesions to the surrounding viscera were even more dense than they were thought to be at the time of operation. The upper portion of the tumor was partially solid, the center of it being filled with broken-down colloid-looking material. The lower portion of the tumor had invaded the mesentery of the transverse colon and one projection of it extended over to the cecum. This portion of the tumor seemed of more malignant nature than any portion examined. A large specimen was taken from this and also the upper portion of the tumor. The spleen was exposed, the notch plainly seen and the lower pole appears normal in consistency and size. The upper portion of the spleen was enlarged four or five times its normal size and firmly adherent to the parietal peritoneum. As much of it as was exposed seemed of normal appearance, with the exception of hypertrophy.

The free border of the right lobe of the liver was very thin and extended about four fingerbreadths below the costal margin. The rest of the liver from palpation appeared very much atrophied and was very hard. This examination plainly showed the futility of any operative removal of the growth and there was little doubt of its malignant character.

Microscopic study of removed sections by Dr. Stuart Graves revealed atypical masses of cells, apparently of lymphoid origin. These cells varied greatly in size and shape. There was little connective-tissue stroma. There were numerous mitoses. (Figs. 1 and 2.)

Microscopic Diagnosis: Lymphosarcoma.

CASE 2.—Mrs. R. C. C., white, aged 30 years, was first seen by us in April, 1927. She had had 3 children and 1 miscarriage 3 years ago. Other than the fact that her father had died of pulmonary tuberculosis, the family history was negative. The present illness began in December, 1926, with sharp pains in the left hip and leg which continued for a month. She then developed pain in the left upper extremity and also in the right upper and lower extremity. There was never any swelling or redness of the joints and very little occasional stiffness of the extremities. There has

never been any elevation of temperature. The tonsils were suspected as the cause of her trouble, and removed, without improvement in her general condition. There have been no other symptoms except amenorrhea for 3½ months. The pains in the extremities continued and she visited one of the "spas" without benefit.

Examination shows a markedly undernourished white female whose skin has a somewhat yellowish tint. The mucous membranes are very pale. The eyes, teeth and throat are negative for any abnormalities, the tonsils being out. The thyroid is not enlarged and there are no enlarged lymph nodes in the neck. The breasts are flabby and contain no tumors. There are no glands in the axilla. The lungs are resonant throughout and there are no adventitious breath sounds. The heart is not enlarged. The apex beat is within the nipple line; there are no thrills or murmurs and the sounds are of fair quality. The abdomen is relaxed. The liver is enlarged, extending 1½ inches below the costal margin. It is smooth and firm and not tender. The spleen extends 2 inches below the costal margin and descends on inspiration. There are no other masses and no tenderness.

Gynecologic examination reveals a markedly relaxed pelvic floor, but no other abnormalities. The glands in the groins are possibly a little enlarged. Reflexes in both legs are active. There is no disturbance of sensation in legs.

Laboratory studies showed: Urinalysis, negative. Blood Wassermann, negative. The blood count was: Hemoglobin, 25 per cent; red cells, 1,550,000; leukocytes, 3350; polymorphonuclears, 55 per cent; lymphocytes, 40 per cent; endothelial cells, 5 per cent. Anisocytosis and poikilocytosis were very evident. Nucleated red cells were present. The stool was negative for blood or parasites on repeated examinations. Roentgen ray examination of the gastrointestinal tract was negative. Dental films showed one area of questionable infection.

On April 5 and again on April 8 blood transfusion was done, giving 600 cc. the first time and 500 cc. the second time, using the Vincent tube method.

The blood count on April 9, 1927 was: Hemoglobin, 55 per cent; red cells, 2,950,000

Pains in the legs were not so severe. The patient had some elevation of temperature.

The blood count on April 12, 1930 was: Hemoglobin, 55 per cent; red cells, 3,310,000; leukocytes, 2800; polymorphonuclears, 57 per cent; lymphocytes, 41 per cent; endothelial cells, 2 per cent; icterus index, 7.5; coagulation time, 4 minutes; bleeding time, 3 minutes; blood platelets, 244,000.

The patient was seen by Dr. Morris Flexner, of Louisville, and a diagnosis of early Banti's disease was made and splenectomy decided upon.

A preliminary transfusion of citrated blood was given and splenectomy done on April 18, 1927. The spleen was about three times the normal size, firm and adherent at the upper pole and also posteriorly. It was freed and delivered and after ligation of the pedicle was removed. A gauze strip was packed into the splenic fossa to control oozing. The patient left the table in mild shock.

The following day another transfusion was given after which improvement was marked. The blood count on April 26, 1927 was: Hemoglobin, 63 per cent; red cells, 3,620,000; leukocytes, 2900; polymorphonuclears, 52 per cent; lymphocytes, 41 per cent; endothelial cells, 6 per cent; eosinophils, 1 per cent.

Examination of the spleen by Dr. Stuart Graves was reported as follows: Specimen consists of a spleen, 17 by 10 by 5 cm.; weight, 450 gm.; beefy red and fairly flabby; capsule taut. A series of paraffin sections, thin and carefully stained, show obliteration of normal landmarks with diffuse

atypical growth of undifferentiated, large, hyperchromatic cells of lymphoblastic type with numerous mitoses.

Microscopic Diagnosis: Lymphosarcoma.

The patient did not recover her strength as she should have, although the wound healed perfectly. She continued to have pains in the legs and irregular fever. The day before she left the hospital the blood count was: Hemoglobin, 50 per cent; red cells, 3,390,000; leukocytes, 2140; polymorphonuclears, 39 per cent; lymphocytes, 54 per cent; endothelial cells, 3 per cent. Nucleated red cells (normoblasts), 7. Myelocytes, 4; red cells show achromia and some poikilocytes and a few microcytes.

The patient died 8 months after her operation. No autopsy was done.

This case is interesting, especially in its resemblance to pernicious anemia, because of the high color index, the leukopenia and the increase in the icterus index. The pain in the extremities also suggests pernicious anemia in which cord symptoms are not uncommon.

Howard's case is similar to this one in some respects and varies only in that in his there seemed to be a remission with later exacerbation of symptoms. His case was a reticulated-cell sarcoma and the one we report a lymphosarcoma.

Summary. 1. We have herein added 2 cases to the literature of sarcoma of the spleen, both being cases of the lymphocytic type.

2. Sarcoma of the spleen may simulate pernicious anemia in its symptomatology and hemocytology.

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CHEMICAL FACTORS REGULATING BLOOD PRESSURE.*

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THE study of chemical substances capable of elevating or of lowering blood pressure is of obvious importance. The isolation and identification of substances in the body which have hypertensive action may lead to a solution of the etiology of essential hypertension, a disease which still remains, in spite of the enormous amount of study expended upon it, a disease of theories. The isolation and identification of substances in the body which have a hypertensive action may lead, we hope, to a satisfactory control of this same disease, which remains also not only a disease of theories but a disease whose mastery is one of the outstanding challenges of today.

* Read at the annual meeting of the American Climatological and Clinical Association, Hot Springs, Va., May 7, 1931.

As we survey the field we cannot but be impressed by the fact that our knowledge of hypotensive substances is more extensive than our knowledge of hypertensive substances. Indeed, I think one may say without contradiction that, while the presence of several substances in the body capable of lowering blood pressure has been established, and such substances have been isolated, yet the only substance having a hypertensive action whose presence in the body has been definitely proved is adrenalin.

The theory that an excess of adrenalin is responsible for the production of arterial hypertension dates from the observations of Neusser,¹⁷ in 1898, and of Vaquez,²¹ in 1904. Vaquez has championed the theory that hypertension is due to an overactivity of the adrenals. In spite of all the work which has appeared in support of this idea, it still remains a theory, since no one has yet proved conclusively that there is an excess of adrenalin in the circulation of patients suffering from arterial hypertension.

In 1922 Labbé, Tinel and Doumer¹⁰ reported a case of arterial hypertension in which a tumor of the adrenal was found at autopsy. Vaquez and Donzelot, in 1926, described a case of paroxysmal hypertension, which was later treated by Laubry with deep Roentgen ray over both adrenals with apparent recovery. Oppenheimer and Fishberg¹⁸ reported, in 1924, a case of hypertension in a young girl, aged 12 years, who showed an adrenal tumor at autopsy. Oberling and Jung, in 1927, described a similar case. Pincoffs,²⁰ in 1929 reported a case of paroxysmal hypertension who was operated upon by Dr. Arthur Shipley and a tumor of the right adrenal removed. One year later the patient was apparently in perfect health and had a systolic blood pressure of 110 to 125. The tumor proved to be a paraganglioma and contained large amounts of adrenalin.

These observations are of extreme importance since they prove that one type of hypertension is due to an excessive production of adrenalin. However, the symptomatology and clinical course of these cases of paroxysmal hypertension is so characteristic and so different from that of the classical picture of chronic essential hypertension that it is taking a long jump to assure that the two conditions are due to the same etiologic factor.

Next to adrenalin, attention has been directed to certain amines as possible causes of hypertension. Several investigators, notably Koessler, have shown that certain amines may be produced by bacterial decomposition of proteins. This has, of course, inevitably led to speculations regarding the absorption of such products from the intestinal tract with a resulting hypertension. One substance, tyramin, has been studied particularly. Tyramin produces a marked elevation in blood pressure and is absorbed readily from the intestinal tract. Its presence in the body has not, however, been conclusively demonstrated, although the recent discovery by

Hare⁷ of a ferment in the liver capable of destroying tyramin is of great interest. The presence of tyraminose in the liver suggests a possible mechanism by which this pressor substance absorbed from the intestinal tract is destroyed and rendered innocuous. Further work along these lines may lead to important discoveries.

We have been interested for several years in a study of guanidin compounds, some of which, as is well known, are powerful pressor substances, while others are equally potent depressor substances. Our observations have been mainly upon guanidin and methyl guanidin, which are pressor substances, and upon glycocyamin (guanidin acetic acid), which is a depressor substance.

In 1927 Weber and I¹² found that in a series of cases of essential hypertension that approximately 50 per cent showed an increase in the blood of some substance giving a color reaction for guanidin. These observations were confirmed by Davis,³ in 1928, and more recently, in 1930, by Pffiffer and Myers.¹⁹ We have now observations upon more than 400 patients with the same results.

Even more striking are our results in cases of chronic nephritis. We have never yet seen a case of chronic nephritis with hypertension, who failed to show an increase in this substance.

In spite of repeated attempts we have not succeeded in proving positively that the substance producing the color reaction is guanidin, and this failure is, of course, a strong argument against the entire conception. One fact, however, is very striking and difficult to explain away—we have never encountered an increase of this substance in the blood of a person with a normal blood pressure.

The question whether any guanidin compounds other than arginin, creatin and creatinin occur in the body has been hotly debated. Most of the methods employed up to this time to isolate guanidin and methyl guanidin are untrustworthy. It is comparatively easy to obtain methyl guanidin from the urine and muscle, but the methods employed use silver salts, which convert creatinin into methyl guanidin, and such methods are now rightly considered faulty. More recently Komarow⁹ has asserted that by using a method free from these objections he has demonstrated the presence of considerable quantities of methyl guanidin in the muscles. This work lacks confirmation as yet, but if correct, is obviously a very important contribution to the subject.

In 1928 we showed that many patients with arterial hypertension whose kidney function when tested by the usual methods is apparently normal, are unable to excrete methyl guanidin in the way that healthy individuals do.¹⁴ These observations have since been confirmed and extended in our laboratory. Their significance is not altogether clear. They may suggest, of course, that such individuals have a peculiar physiologic anomaly of the kidneys, which consists in an inability to excrete methyl guanidin normally. Such an anomaly could obviously lead to a retention of methyl guanidin

with a resulting hypertension. On the other hand, this inability to excrete methyl guanidin may be merely a very delicate test of early renal insufficiency, since in chronic nephritis inability is much more marked and striking than in what we term essential hypertension. More observations over a longer period of time are necessary before we can begin to draw conclusions.

When we turn to a consideration of the depressor substances present in the body we find that a larger group have been definitely isolated and identified and still others are either isolated or their presence strongly suspected. This particular phase of the subject has been followed with intense interest not only by pharmacologists, but particularly by internists who have hoped that some of these substances might prove effectual agents in the control of arterial hypertension.

One of these substances, histamin, has been the subject of a great deal of investigation. The observations of Abel and Kubota, of Koessler and of Dale and his associates have been of great importance. This exceedingly powerful and also highly toxic substance we now know, thanks to labors of Dale and his coworkers, is present in most of the tissues of the body, not merely in traces, but in considerable quantities. The significance of this fact is not fully understood, but the pharmacologic antagonism of histamin to adrenalin suggests a possible normal mechanism of blood pressure control. As a therapeutic agent, however, for the control of high blood pressure histamin is disappointing. It is a highly toxic substance, it reduces blood pressure too rapidly with frequent distressing symptoms and it also has the effect of often being followed by a subsequent rise in blood pressure above the initial level.

Another substance which has a profound depressor effect upon the blood pressure is cholin, whose presence in the body has been definitely demonstrated. More recently another closely allied substance, acetocholein, was isolated by Dale and Dudley.² Acetocholein is an extremely powerful depressor substance, being approximately one thousand times as powerful as cholin. Acetocholein is relatively unstable and, while its presence in the body was suspected for some time, it remains for Dale and Dudley to demonstrate its actual occurrence. The isolation of this substance is a striking proof of the skill and ingenuity of these investigators. Drury and Szent-Gyorgi⁴ found that adenylic acid and adenosin caused a fall of blood pressure. Adenylic acid is present in the blood in skeletal muscle, in heart tissue, in the brain and in the kidneys.

Glycocyamin, or guanidin acetic acid, is a very interesting substance. It differs from creatin only in the absence of a methyl group, and while creatin has no characteristic effect upon the blood pressure, glycocyamin is a powerful depressor substance. It

is relatively nontoxic, it is effective when taken by mouth and it also, as Ginsberg and Stoland⁵ have shown, causes a marked increase in coronary flow. The presence of glycoeyamin in the body has not been demonstrated, although Karashima⁸ has recently described a ferment in the liver capable of oxidizing it.

Our especial interest in this subject of depressor substances began with the study of the depressor effect of certain liver extracts. We feel that the effects of these extracts was not due to either histamin or cholin, but the evidence was not conclusive. In 1927 Best, Dale, Dudley and Thorpe,¹ in a series of investigations, isolated histamin in considerable quantities from these liver extracts, and were inclined to attribute their depressor effects to the presence of histamin. Vincent and Curtis²² questioned these conclusions, but since Dale and his coworkers had definitely isolated histamin, and their critics could produce no other depressor substances, the prevailing opinion was that these extracts owed their activity to histamin. We have continued our investigations of this problem the past 4 years and feel that we have definite evidence of the existence of a depressor substance in the tissues which is neither histamin, cholin, nor acetyl cholin. In 1929 Weber and I¹⁶ showed that when liver tissue was treated in two different manners an extract having the pharmacologic properties of histamin could be obtained from one fraction, while from another fraction an extract could be isolated which showed no chemical tests for histamin and also differed in its pharmacologic behavior.

Histamin, as is well known, produces a fall of blood pressure when injected intravenously into dogs, but under certain standard conditions causes a rise of blood pressure in rabbits. One of our extracts which gave a positive Pauly reaction for histamin produced a rise of blood pressure in rabbits, while the other extract which gave a negative Pauly reaction caused a fall in blood pressure in these animals. When these two extracts were mixed in proper proportions and injected into rabbits no change in blood pressure occurred. This latter observation cleared up a question that had puzzled us for a long time—why certain liver extracts produced a marked fall of blood pressure in dogs, but had no effect upon the blood pressure of rabbits.

Later we found this histamin-free depressor substance present in considerable quantities in the brain and we have employed the brain as the source of supply for most of our later experiments. By a process of precipitation with acetone and purification with copper and mercury we have obtained a thick viscid fluid, which is apparently the active principle. When precipitated under certain conditions it comes down as a fine white granular crystalline-like substance, which, however, probably because of its marked hygroscopic properties, is changed almost immediately into a thick oily-like liquid. It is, however, apparently not an oil, for it is insoluble in the ordinary oily solvents.¹⁵

This substance we have found present in considerable quantities in the blood. This finding we think is of interest since it suggests that it may play a rôle in maintaining the blood pressure at a proper level, since its absence or presence in insufficient amounts could conceivably lead to an elevation in blood pressure. Another finding of some interest is the presence of a positive Sakaguchi reaction in the purest solutions we have obtained, indicating the presence of a guanidin compound.

We have as yet made no extensive studies of the therapeutic effects of those pure histamin-free extracts. We only know that when injected they produce a temporary fall of blood pressure in normal individuals and in certain hypertensives.

This summary of certain chemical factors having hypertensive and hypotensive action, indicates that much information has been obtained and still more is desirable. The whole subject is one of great interest, and it requires great self control not to wander off into a maze of speculation. But as we survey the history of the many diseases which we now understand fairly clearly, we are struck, I think, by the fact that it is one thing to observe, but quite another to interpret.

Conclusions. The only pressor substance whose presence in the body has been demonstrated without any doubt is adrenalin. Guanidin compounds capable of elevating the blood pressure may exist in the body, but their presence has not been unequivocally demonstrated. There is some evidence that they are actually present but more proof of their existence must be given before we can definitely state that such is the case.

Several depressor substances have been demonstrated in the body. Histamin, cholin, acetylcholin, adenylic acid and adenosin have been definitely isolated. There is in addition another substance with powerful depressor action which has not been identified but which is apparently widespread in the body.

The physiologic rôle of these depressor substances offers a wide field of research. Their possible therapeutic effects, either singly or in combination may open up a new field of therapeutic endeavor.

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THE STUDY OF YELLOW FEVER BY A PROTECTION TEST IN MICE.

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THE prevalent idea about yellow fever seems to be that it has been banished from most of the world and will soon be extinct. The studies of the International Health Division of the Rockefeller Foundation now under way in West Africa and South America show that this view is overoptimistic and that long campaigns will have to be waged before the disease is conquered in the endemic areas of these countries. In the meanwhile, the danger in the situation is being accentuated by the increase of commerce with the endemic regions, the greater rapidity of travel by land, sea, and air, and the rising susceptibility of the population in the regions which have already been freed of yellow fever. On the bright side of the picture is our greater power to control the disease owing to the improvement in methods of diagnosis and of epidemiologic study made possible by the availability of experimental animals.

The regions in which yellow fever is persisting are so vast that indiscriminate intensive control measures throughout the whole of the suspected regions, with their many port cities and populous interior centers, would seem at present to be impossible. It is conceivable, however, that the disease could be suppressed if control efforts could be concentrated in the permanent endemic centers. It has not been possible to locate the endemic regions accurately with the older methods of clinical observation.

In endemic areas epidemics are infrequent, or absent, and only an occasional case, usually in a foreigner, comes to the attention of the authorities. The disease is kept alive in children who suffer with so mild a form that a clinical diagnosis of yellow fever is rarely possible. It is unfortunately true that in most such regions there are almost no well-trained physicians and reliable reports can scarcely be expected. The situation seems to be similar to that revealed in parts of the United States with regard to poliomyelitis by Aycock, Kramer¹ and others.

The bright points in the recent history of yellow fever are: (1) The demonstration by Walter Reed and his colleagues in Havana in 1901, that the disease was conveyed by the *Aedes aegypti* and that the causative organism behaved like a filtrable virus; (2) the demonstration by Stokes, Bauer and Hudson² in West Africa in 1927 that the common monkey of the zoölogical gardens, *Macacus rhesus*, was susceptible to the disease, and (3) the finding of Theiler³ in 1930 that a neurotropic strain of the virus could be produced by intracerebral inoculation of white mice, so that we now have two susceptible animals.

An effective method of delimiting the endemic areas of yellow fever is to collect the sera of adequate numbers of children at key places and to test these for power to protect experimental animals against yellow fever virus. This has been done for several centers in West Africa by Beeuwkes, Bauer and Mahaffy⁴ who used rhesus monkeys. The tests showed a wide variation in the percentage of immune children in the several localities and indicated whether yellow fever had been present in recent years. This valuable method cannot be used on a scale large enough to permit the detailed mapping of the endemic areas needed for a true appreciation of the distribution of yellow fever or as a guide for control measures. The discovery by Theiler³ of the susceptibility of the white mouse to yellow fever when inoculated intracerebrally has given us the animal needed for extensive surveys. He showed that yellow fever in the mouse took the form of an encephalitis, and that the mixture of human immune serum with the virus injected would inhibit or defer the infection. After many passages through mice the virus became highly virulent for these animals, causing death as a rule on the fifth or sixth day after inoculation, and lost its power to kill rhesus monkeys, although it continued to produce fever in these animals, and in these respects it assumed the character of a fixed virus.

In order to adapt the protection test in mice to the needs of the field studies which we have carried out, Sawyer and Lloyd⁵ sought to make the test more sensitive and regular. They found that fatal encephalitis could be produced by yellow fever virus when introduced intraperitoneally if, at the same time, a mild irritant was injected intracerebrally to localize the virus. Further, if immune serum in suitable amount was injected into the abdomen with the virus, the animal was protected. The technique now being used in the routine application of this intraperitoneal protection test is as follows: The mice are lightly etherized and are given an intracerebral injection of 0.03 cc. of 2 per cent starch in physiologic sodium chlorid solution. They are then given an intraperitoneal injection of 0.2 cc. of a 20 per cent suspension of brain tissue from infected mice and 0.4 cc. of the serum to be tested. In the control injections normal human serum is given in the place of the unknown serum. A group of 6 mice is used as a unit in the examination of each specimen of blood. The mice in the control groups die as a rule from 5 to 10 days after inoculation, usually after 5 or 6 days. The groups receiving non-immune sera die like the control animals, while those receiving potent immune sera should survive for at least 10 days.

The survey of endemic areas with the help of the protection test in mice is now under way. Sera are being collected under a systematic plan in West Africa, Brazil and elsewhere by our field staff, and are being examined in Lagos, Nigeria, West Africa, in Bahia, Brazil, and in our laboratory in New York. Later we shall know how widespread yellow fever infection really is, and where governments can most intelligently concentrate their control work.

The intraperitoneal protection test in mice may be used also in the titration of immune sera with regard to protective power, and is useful in the study of individual cases of yellow fever. It may help in deciding the diagnosis late in the disease or during convalescence. A laboratory worker recently contracted yellow fever while handling virus from mice, and his case was studied by Berry and Kitchen.⁶ They had the coöperation of Dr. Max Theiler, who made tests of the patient's serum by the intraperitoneal method in mice and also injected specimens of blood intracerebrally into mice. The serum of the patient showed no protective power on the second and third days of the disease, but there was distinct, though slight, protection on the fourth day. The specimens obtained on the fifth and sixth days gave definite protection. Mice were infected by the blood specimens drawn on the first, second, and third days of illness, but not by those taken on the fourth or fifth days. Rhesus monkeys were inoculated with blood taken on the first, fourth and fifth days, and all three came down with yellow fever. Thus, with the highly sensitive protection test in mice and the inoculation of the very susceptible *Macacus rhesus* monkeys, it was possible to demonstrate

the presence of active virus and immune bodies against that virus in the same specimens of blood—those taken on the fourth and fifth days. The diagnosis of yellow fever was proved by each of the three procedures mentioned, as the serum had been tested shortly before the illness and found to be devoid of antibodies protective against yellow fever.

Summary. 1. Yellow fever still persists in South America, and is widely prevalent in West Africa.

2. In the endemic areas cases are few and apparently sporadic, but the virus when carried outside such areas gives rise to true epidemics.

3. The immunity following an attack is solid and permanent.

4. The protection test in monkeys or in mice will show the presence or absence of immunity.

5. The boundaries of an endemic area may be drawn by examining the blood serum of children, and determining whether or not any of them are immune and so establishing the presence of yellow fever in the area within the life time of the children.

6. The test with mice is more delicate than that with monkeys and may be used to titrate immune sera after an attack or after vaccination.

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THE PRESENCE OF HETEROPHILE ANTIBODIES IN INFECTIOUS MONONUCLEOSIS.*

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THE term *heterophile antibody* applies to antibodies having the capacity to react with certain antigens, which are quite different from, and phylogenetically unrelated to the one instrumental in

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producing the antibody response. Their existence became recognized largely through the work of Forssman in 1911,¹ whose name has been attached to antigens capable of eliciting the heterophile response. Since their discovery they have been studied experimentally by many investigators, to which Davidsohn's exhaustive review² bears testimony, but only recently have the principles involved found clinical application. No attempt will be made in this paper to review the development of knowledge of heterophile antigens and antibodies, for the subject is a complex one, probably still in its infancy, and furthermore the reader may be referred to Davidsohn's review,² and recent textbook articles by Bull,³ and Topley and Wilson.⁴ However, a few definitive statements relative to the nature of the phenomena involved may be warranted.

Briefly it has been shown that certain substances such as emulsions of cells obtained from the organs of the guinea pig, cat, dog and horse, a number of other mammals, birds and certain fish, when injected into an appropriate animal such as the rabbit, are capable of giving rise to, not only specific antibodies, but also nonspecific antibodies which are demonstrable in varying degree in the form of hemolysins and agglutinins for sheep cells. Chemically, the antigen capable of eliciting this response has been defined as lipoid-protein complex. The whole complex is necessary for the production of heterophile antibodies, whereas the lipoid fraction, which can be extracted with alcohol, reacts with antisera *in vitro*, but is incapable of producing heterophile antibodies. In other words, the antigenic capacity depends on the integrity of the lipoid-protein complex and the extracted lipoid affords another example of a haptene. Apparently the substances which contain the heterophile or Forssman antigen are widespread throughout the animal kingdom, representing a growing list, often referred to as the so-called *guinea pig* group of substances. In contrast, stands the so-called *rabbit group*, representing substances in which the Forssman antigen has not been found, such as the organs of the rabbit, man, ox, rat, etc.

Only a few pathogenic bacteria are known to belong to the guinea pig group and probably for this reason heterophile antibodies have not been demonstrated in appreciable amounts among patients suffering from disease induced by most bacterial agents. Nevertheless, the phenomenon of heterophile antibody production may occur in human beings into whom substances containing the heterophile antigen have been injected. This has been shown by Davidsohn,^{5, 6} who has demonstrated the enhanced presence of lysins and agglutinins for sheep cells in the serum of patients who had been injected with horse serum. As a corollary to this finding Davidsohn also made the important observation that the average titers for agglutinins and hemolysins were very much higher among patients who had been injected with horse serum and who subsequently developed

serum disease, than among those who did not develop allergic symptoms. In cases of serum disease produced by the injection of *bovine* serum, heterophile antibodies were not found.

Following the publication of Davidsohn's observations on the presence of heterophile antibodies in serum disease, it seemed to us that a study of this type could be directed against a number of clinical conditions in which heterophile antibodies might exist. Our attention was first turned to cases of rheumatic fever, owing to the resemblance which many of the symptoms of this disease, such as skin eruptions, glandular enlargement and polyarthritis bear to serum disease; but we were unable to demonstrate a consistent or an appreciable increase in the heterophile antibody content of the sera from patients suffering from this condition. In the course of this study a number of controls from individuals suffering from serum disease and a variety of other clinical conditions were assembled. Quite by accident it was discovered that heterophile antibodies (demonstrable in the form of sheep cell agglutinins) were present in a specimen of serum from a patient, ill with infectious mononucleosis, in much higher concentration than has been described in serum disease or in any other clinical condition which we have studied. Subsequently we have confirmed this finding in the acute phases of 3 other cases of infectious mononucleosis and our observations upon this disease furnish the basis of this report.

Methods. We have employed the methods used by Davidsohn for determining the presence and titer of sheep cell agglutinins and hemolysins.⁵ The technique is quite simple.

Sheep Cell Agglutinins. Sera, obtained as for a Wassermann test, were inactivated for 15 minutes at 55° C.* Dilutions of inactivated sera, ranging from 1 to 4 to 1 to 32 (or higher if the heterophile antibody content was suspected to be present in unusual concentration), were set up in 0.5 cc. portions. To these 0.5 cc. of a 2 per cent suspension of sheep cells† were added, followed by 1 cc. of salt solution, thus bringing the total volume in each tube to 2 cc. The test tubes were shaken and placed in the water bath at 38° C. for 1 hour, left in the icebox overnight and on the following morning were read, after each tube had been inverted three times with its mouth covered by the finger tip. A series of tubes which had been recently inverted and then allowed to settle for a few minutes is shown in Fig. 1. The titer of sheep cell agglutinins in this instance was 1 to 128.

For the sake of conformity with previous work, the readings have been recorded in terms of the original dilution of the 0.5 cc. of sera added to each tube. With the subsequent addition of 0.5 cc. of the suspension of sheep cells and 1 cc. of saline, the dilution of serum becomes much higher so that actually the tube designated 1 to 4 contains 0.12 cc. of serum in

* Experiments were performed upon the optimum time of inactivation, which proved to be between 15 and 30 minutes. Samples of sera inactivated for longer periods of time seemed to show diminution of heterophile antibody content.

† The sheep cells, which were obtained fresh each week, had been washed three times in saline and were allowed to stand in saline in the icebox for a period of 2 to 5 days before using. We are indebted to Dr. G. H. Smith and Mrs. Edna Lyons, of the Department of Immunology, Yale University for supplying us with washed sheep cells during the course of this work.

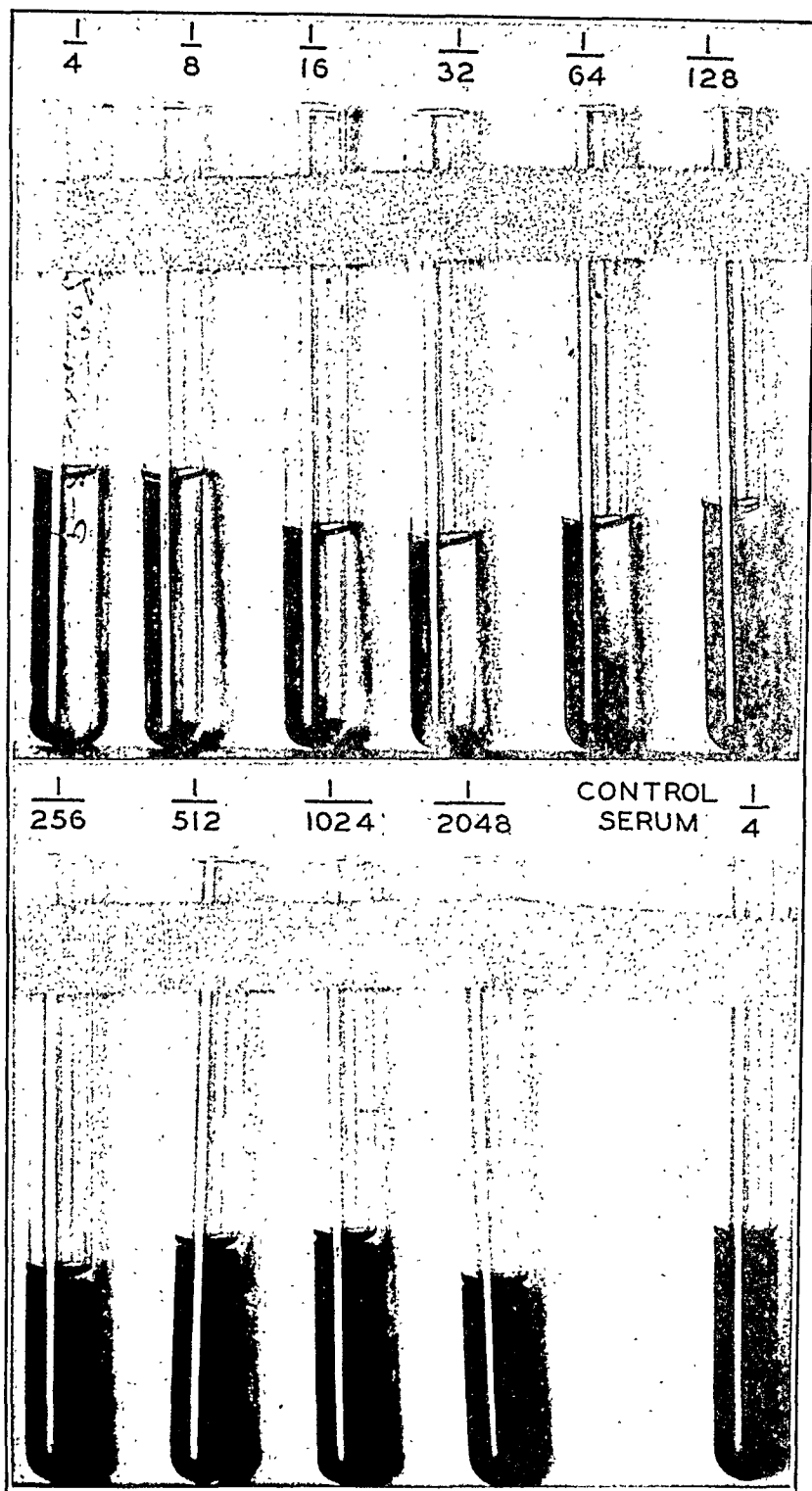


FIG. 1.—Sheep cell agglutinin determination. A series of tubes containing sheep cells and dilutions of serum, from a patient with infectious mononucleosis. The titer is 1 to 128. A normal control serum (dilution, 1 to 4) is shown on the right.

2 cc. of cell suspension; that designated 1 to 8 contains 0.06 cc. of serum, in 2 cc. of suspension. Legends for recording the readings are given in the following terms:

+++ firm disk.

++ disk easily broken into large flakes.

+ fine agglutination.

= barely perceptible, but definite agglutination.

Sheep Cell Hemolysins. In the observations recorded below all of the results have been given in terms of sheep cell agglutinins. Sheep cell hemolysins were found to parallel the agglutinin content with such regularity that the former have not been recorded. In many of our earlier determinations both tests were run and were found to serve as a rough check, one for the other.

Hemolysin tests were run as follows: Original dilutions of 0.5 cc. of inactivated sera, similar to those used in the agglutinin tests, were employed. To these 1 cc. of guinea pig complement in a dilution of 1 to 30 was added, then 0.5 cc. of a 2 per cent suspension of sheep cells, followed by 1 cc. of saline, thus bringing the total volume to 3 cc. in each tube. The tubes were shaken, placed for 1 hour in a water bath at 38° C. and read.

Results. *Sheep Cell Agglutinins in Normal and General Hospital Patients.* Before attempting to interpret our findings in different clinical conditions, it seemed important to assemble a large group of control cases, including as many normal individuals as possible, in order to obtain a base line for subsequent studies. Similar work on the measurement of heterophile antibodies in large groups of normal individuals or hospital patients may be briefly reviewed as follows:

The presence of hemolysins and agglutinins for sheep cells in low dilutions of supposedly normal human sera has been repeatedly observed.^{5, 6, 7, 8} Some investigators⁹ also give figures to show that their occurrence in human beings may be influenced somewhat by the blood group of the individual from which the serum is obtained. In Davidsohn's first studies⁵ on the presence of sheep cell agglutinins in normal individuals, representing a series of 450 adults, he found them to be present in the low dilution of 1 to 4 in 4.2 per cent. Subsequently,⁶ in studying a larger series (which included 850 adults and children) he found 9 per cent to possess agglutinins for sheep cells in dilutions of 1 to 4, only a few in dilutions of 1 to 8; and none in higher dilutions. He believed the higher percentages, present in the second series, which included children, to be due to the increasing number of therapeutic immunizations with various sera administered during childhood. Agglutinins for the blood cells of other animals were studied by this author who records the presence of ox, guinea pig and rabbit blood cell agglutinins in a much higher percentage of normal individuals, thus placing sheep cells in a rather unique position from the standpoint of their reactions with human sera.

A more extensive study on the incidence of *nonspecific* agglutinins in man is that of Friedberger and his coworkers.¹⁰ These

investigators have determined the presence and concentration of sheep cell hemolysins and rabbit cell agglutinins in individuals of different age groups, finding that both sets of antibodies were absent at birth, that they were demonstrable in low concentrations among 20 per cent of infants during the first year of life; 60 per cent by the fifth year, and 90 per cent by the tenth. This high incidence remained throughout adolescence and early adult life, but subsequently fell slowly to about 20 per cent in old age. In interpreting these findings the German investigators have raised the question as to whether defensive antibodies may not be formed in growing children as an expression of *immunologic maturation*.

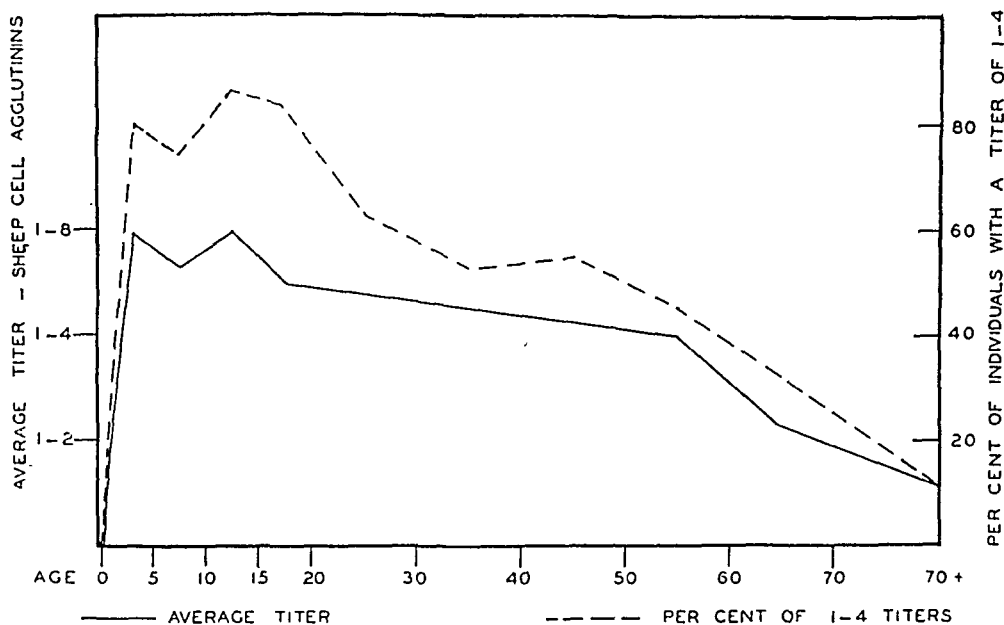


FIG. 2.—The age distribution of sheep cell agglutinins in sera from a series of 275 general hospital patients.

Our own control studies on the presence of sheep cell agglutinins in human sera have been made with particular reference to their concentration in different sets of clinical conditions. We have not succeeded in assembling a very large series of normal controls, but in our series of 275 general hospital patients there were many individuals in whom there was no reason to suspect an infection or any deviation from the normal antibody content of their sera. An accurate history in each individual with regard to the injection of horse serum for therapeutic or prophylactic purposes was not obtained. However, in none of the 275 control patients, included in this series, were sheep cell agglutinins found in unusually high concentration. We attempted to secure a wide age distribution in this group by including placental blood, infants under 1 and 5 years, and adequate groups of individuals representing different decades

of life up to the age of 70. The results are shown in Fig. 2. Here it will be seen that in none of the 10 samples of placental or cord blood were sheep cell agglutinins present. There is a rapid rise during the first 5 years of life reaching an irregular peak between 5 and 15, at which time the average concentration is close to 1 to 8; it then undergoes a gradual decline. If expressed in terms of the percentage of individuals in whom sheep cell agglutinins were demonstrable in a concentration of 1 to 4 it will be seen that there is a sharp rise from zero at birth to 80 per cent by the fifth year, and 86 per cent by the fifteenth year. It then declines to 60 per cent by the thirtieth year; 54 per cent by the fortieth; and 40 per cent by the sixtieth year, etc. Our findings show the relative frequency with which low concentrations of sheep cell agglutinins are usually found in human sera, and furnish a rough base line on which deviations from the average curve may be ascertained. They are essentially in agreement with those of Friedberger *et al.*,¹⁰ who in a similar manner have studied the age distribution of sheep cell hemolysins and rabbit cell agglutinins in a group of hospital patients.

Sheep Cell Agglutinins in Various Clinical Conditions. In Table 1 are shown some of the clinical conditions in which our determinations of sheep cell agglutinins have been made. In Group II, which includes a number of different examples of infectious disease, there seems to be a slight tendency for maximum titers to run above the usual figures (Fig. 2), although only in a single instance was a titer of 1 to 32 recorded. Seven cases of serum disease are shown in Group IV, in which a very appreciable increase of the agglutinin titer was found in 90 per cent of the cases. In Group V are recorded the findings in the 4 cases of infectious mononucleosis which we had the opportunity of studying. In all of them titers are recorded which are higher than those observed in our most severe cases of serum disease, in one instance representing an original dilution of 1 to 1024.* A number of examples of other blood dyscrasias have been assembled in Group VI, including 2 cases of chronic lymphatic leukemia. In none of these, however, was an increase in the sheep cell agglutinins observed, except in a single case which will be discussed more in detail later. These findings show that the presence of a high concentration of heterophile antibodies is a fairly consistent feature of infectious mononucleosis, and that apart from the cases of serum disease, appreciable amounts of heterophile antibodies have not appeared in our controls, except in one notable case.

The Relationship of Sheep Cell Agglutinins to the Symptomatology of Infectious Mononucleosis. Brief clinical details of 2 of our 4 cases are given in the following case reports. The temperature

* Absorption determinations were run in one of our cases of infectious mononucleosis. It was shown that the agglutinins could be absorbed by sheep cells.

TABLE 1.—SHEEP CELL AGGLUTININS IN MISCELLANEOUS CONDITIONS, SERUM DISEASE AND INFECTIOUS MONONUCLEOSIS

Group.	Type of case or diagnosis.	No. of cases.	Dilutions of patient's serum.							
			1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1024
I.	Normal.	11	+	+	—	—	—	—	—	—
II. Infections	Tuberculosis	15	+	+	—	—	—	—	—	—
	Syphilis	6	+	+	—	—	—	—	—	—
	Rheumatic fever and	12	+	+	—	—	—	—	—	—
	rheumatoid arthritis	13	+	+	—	—	—	—	—	—
	Streptococcus infections	2	+	+	—	—	—	—	—	—
	Vincent's infections	1	+	+	—	—	—	—	—	—
	Lung abscess	11	+	+	—	—	—	—	—	—
	Miscellaneous infections	11	+	+	—	—	—	—	—	—
									
	Minimum									
III.	Bronchial asthma	4	+	+	—	—	—	—	—	—
	Miscellaneous conditions	11	+	+	—	—	—	—	—	—
IV. Serum disease	Severe serum disease	3	+	+	—	—	—	—	—	—
	Mild serum disease	4	+	+	—	—	—	—	—	—
V. Infectious mononucleosis	Early	1*	+	+	—	—	—	—	—	—
	Height	4*	+	+	—	—	—	—	—	—
	Late	3*	+	+	—	—	—	—	—	—
VI. Other blood dyscrasias	Pernicious anemia	4	+	+	—	—	—	—	—	—
	Purpura hemorrhagica	2	+	+	—	—	—	—	—	—
	Lymphatic leukemia	2	+	+	—	—	—	—	—	—
	Mycogenous leukemia	2	+	+	—	—	—	—	—	—
	Hodgkin's disease	1	+	+	—	—	—	—	—	—
	Aplastic anemia (?)	1	+	+	—	—	—	—	—	—

* Representing a total of 4 cases.

curves, blood counts, and heterophile antibody titers are also shown in Figs. 3 and 4.

Case Reports. CASE 1.—Fe, a white, male, medical student, aged 22 years, was admitted to the New Haven Hospital on February 7, 1930,

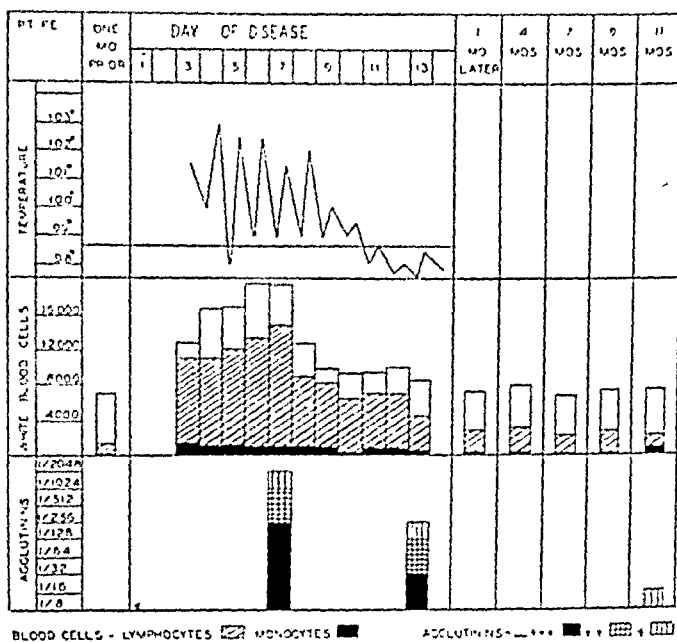


FIG. 3.—Case 1. Infectious mononucleosis.

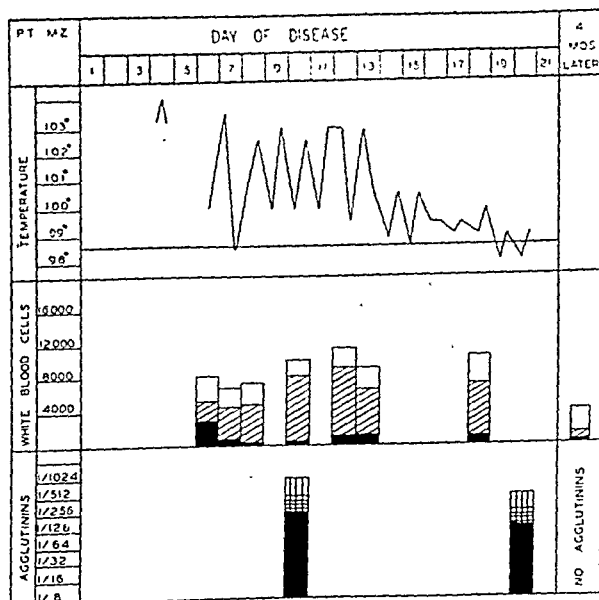


FIG. 4.—Case 2. Infectious mononucleosis. Legends as in Fig. 3.

complaining of malaise, headache, fever and swollen and tender glands. He was a member of the class in clinical microscopy and as such had performed a number of leukocyte and differential counts upon himself 1 month prior to the onset of his illness. Fortunately we had preserved one of these smears which showed a normal differential count.

For a period of 10 days prior to the development of acute symptoms he had been feeling below par. Three days before admission he felt weak and noticed that the glands in his neck and axilla were swollen. Apparently he had not suffered from sore throat.

On admission his temperature was found to be 100° F. The throat was red, but there were no lesions in the oral cavity. There was marked enlargement of cervical lymph glands and slight redness of the overlying skin; the axillary and inguinal lymph glands were also enlarged. The total white blood cell count was 12,800, of which 75 per cent were lymphoid cells, and 13 per cent were monocytes. A throat culture showed an essentially normal flora. The blood culture was negative. On the day after admission he complained of chilly sensations, some photophobia, and hyperesthesia over the skin of the neck. Four days later the temperature began to fall and the lymph glands to recede in size. His course and subsequent blood counts are shown in Fig. 3.

On the seventh day of his illness sheep cell agglutinins were found in this patient's blood to the unusually high dilution of 1 to 1024; on the thirteenth day they were present in a dilution of 1 to 128. The presence of other agglutinins was also investigated in samples of serum obtained on the seventh and thirteenth days of his disease. Tests were made against *Bacillus typhosus*, *Bacillus paratyphosus* A and B, *Bacillus proteus* X-19 and *Brucella abortus*. Agglutinins were not demonstrated for any of these organisms in dilutions of 1 to 20 or higher.

After his discharge from the hospital, blood counts were obtained at intervals of 2 to 4 months. A slight increase in monocytes was noted in three of these counts. Sheep cell agglutinins, when tested 11 months after his illness, were found to be within normal limits.

The interesting feature of this case was the extraordinary high titer to which sheep cell agglutinins were demonstrated during the early stages of a relatively short, febrile illness, together with the fact that the titer had begun to fall with the subsidence of symptoms. The blood count continued to show a slight increase of monocytes almost a year after his illness, but at this time sheep cell agglutinins had fallen to within normal limits.

Details of another case appear below, and are also shown in Fig. 4.

CASE 2.—Mz, a white, female, medical student, aged 21 years, was admitted to the New Haven Hospital on October 25, 1930, complaining of fever.

She gave a previous history of having had frequent attacks of tonsillitis. A week prior to admission she had had a slight sore throat; 2 days later her temperature had been 101° F., and later 104° F.

On admission the patient was slightly jaundiced; there was diffuse redness of the pharynx and generalized glandular enlargement. The liver and spleen were easily palpable. The total white blood cell count was 8000 per c.mm., with 65 per cent lymphoid cells and 12 per cent monocytes. The throat culture showed many hemolytic streptococci; an occasional spirillum and fusiform bacillus was seen in the stained smear. Her subsequent course is shown in Fig. 4.

The jaundice became more intense, and on the tenth day of her disease, the icteric index was 36; the van den Bergh gave a positive indirect reaction, quantitatively equivalent to 6.25 mg. of bilirubin per 100 cc. of blood.

A liver function test, performed by the injection of bromsulphalein at this time, showed the presence of 55 per cent of the dye in the serum 5 minutes after injection and 20 per cent 30 minutes after injection.

After running a febrile course, which in all lasted about 15 days, there was a rapid subsidence of symptoms, with diminution in the size of the glands. The mononucleosis was still marked on the eighteenth day of the disease. Four months later the blood findings were essentially normal except that monocytes numbered 8 per cent.

At the height of her illness sheep cell agglutinins were present in a titer of 1 to 512; during early convalescence the titer was 1 to 256. Four months later agglutinins were absent.

Sheep Cell Agglutinins in Conditions Other than Serum Disease and Infectious Mononucleosis. In one of Davidsohn's articles the authors call attention to the fact that a high titer of sheep cell agglutinins may rarely occur in certain pathologic conditions other than those in which horse serum has been injected, recording a single instance of a patient receiving insulin injections, in whom a titer of 1 to 64 was observed.¹¹ Among the many examples of different pathologic conditions which we have studied, a titer above 1 to 32 was not observed, except in our cases of serum disease and infectious mononucleosis. There was, however, one notable exception which was an obscure case terminating fatally. Clinical details of this case are shown briefly in Fig. 5 and in the following case report:

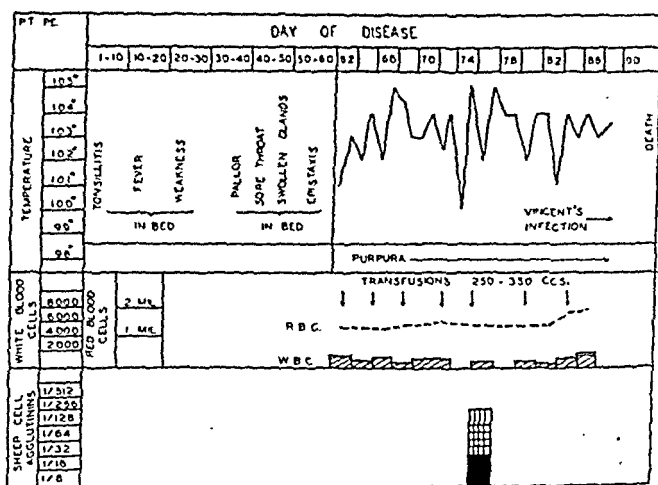


FIG. 5.—An obscure case terminating fatally in which sheep-cell agglutinins were found shortly before death in a titer of 1 to 128. Legends as in Fig. 3.

Case 3.—Pe, an Italian female, aged 19 years, was admitted to the New Haven Hospital on October 16, 1930, complaining of fever, sore throat and weakness. She had apparently been suffering from these symptoms for a period of 2 months. On examination there was marked pallor and some emaciation. The tonsils were enlarged as were also some of the regional, cervical lymph glands, but this was not pronounced. The spleen

was palpable. An eye ground examination revealed retinal hemorrhages, although bleeding was not particularly prominent elsewhere. Blood cultures were consistently negative.

The initial examination of the blood showed 1,200,000 red cells and 1200 white cells, with an absence of polymorphonuclears. The platelets numbered 75,000 and 80,000 on two examinations. Subsequent blood findings are recorded in Fig. 5.

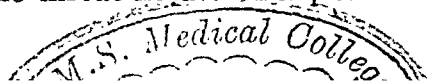
The patient's course was steadily downhill. Two weeks after admission she developed an ulcerative lesion on the right tonsil from which Vincent's spirilla and fusiform bacilli were demonstrated. On the eighty-ninth day of her disease she was discharged from the hospital against advice and died at home a few days later. A satisfactory diagnosis of this case was not reached. In many respects the white blood cell picture recalled that of agranulocytic angina, although the severe anemia spoke against this, and the case has been listed by us as either an example of *aleukemic leukemia* or *aplastic anemia*.

A single determination of the agglutinins for sheep cells was made on the seventy-fifth day of her disease. They were found in a serum dilution of 1 to 128. Prior to this determination she had received a number of blood transfusions (Fig. 5). We do not know what effect this may have had upon the heterophile antibody content of her serum. The patient was Group B, and the cells of this group do not contain the heterophile antigen.¹²

Observations on the Relation of Vincent's Infection to Infectious Mononucleosis. Although the causative agent of infectious mononucleosis is unknown, many bacteria have been incriminated, notably members of the streptococcus group, diphtheroid bacilli, and Vincent's organisms. The association with bacteria thought to cause lesions in the mouth and throat is strong owing to the frequent presence of tonsillitis and oral lesions as an initial symptom of the disease. Recently, however, several observers have raised the question as to whether the disease may not be due to a vibrio. Nyfeldt¹³ has reported the isolation of such an organism from the blood of a patient ill with infectious mononucleosis. Gorham, Smith, and Hunt¹⁴ have also assembled evidence, through the inoculation of guinea pigs, to show that a vibrio may be of etiologic import.

We have not gathered data which have bearing upon questions of the etiology of infectious mononucleosis, except perhaps a few observations which concern the relationship of Vincent's organisms to this disease. This possible relationship has been approached from three angles: (a) The incidence of Vincent's organism in the throats of our small series of patients; (b) an estimation of heterophile antibodies in serum from control cases of Vincent's angina; (c) tests to establish whether or not Vincent's fusiform bacilli contain the heterophile antigen.

(a) *The Incidence of Vincent's Organisms.* From 3 of our 4 cases of infectious mononucleosis, Vincent's organisms were obtained, as follows: Patient 4 (Pn) had an ulcerated lesion on the tonsil from which spirilla and fusiform bacilli could be demonstrated in large numbers. The throat flora of this patient was otherwise not



remarkable. In Patients 2 (Mz), and 3 (Bd), Vincent's organisms were demonstrated in smears from the gums but not in large numbers. In both of these patients the tonsils were inflamed and appreciable numbers of hemolytic streptococci were present in the throat cultures. In Patient 1 (Fe), Vincent's organisms were not found; there were no appreciable tonsillar lesions, and the throat flora failed to show any abnormalities.

(b) *The Determination of Heterophile Antibodies in Vincent's Angina.* Two cases suffering from ulcerative lesions of the mouth, from which large numbers of spirilla and fusiform bacilli could be demonstrated, are included among our series of controls in Table 1. In neither of them were sheep cell agglutinins demonstrable in the serum. It follows, therefore, that if one assumes that Vincent's organisms are in any way responsible for the disease known as infectious mononucleosis, one must also assume that a far more extensive antibody response is elicited in this disease than is seen in the usual case of Vincent's angina.

(c) *Tests to Determine Whether or not Vincent's Fusiform Bacilli Contain the Heterophile Antigen.* Two rabbits were inoculated with suspensions of living organisms from a stock strain of fusiform bacilli.* In both rabbits specific agglutinins for the strain of fusiform bacillus employed as an antigen were rapidly developed in high titers. In neither antisera were heterophile antibodies (demonstrable as agglutinins for sheep cells) detected at any time during the process of immunization. It is, perhaps, unfortunate that we did not use a strain which had been isolated from one of our cases of infectious mononucleosis, and also that suspension of spirilla were not tried for the immunization experiments, but the difficulty of growing these organisms precluded the determination of these points.

Certain complexities arise in the interpretation of this experiment largely because of our limited knowledge of the properties of Vincent's organisms, for the relationship between the spirilla and fusiform bacilli is not clear. However, it has seemed somewhat pertinent to us that the particular strain of fusiform bacilli which we did test, proved to be one which failed to elicit the slightest degree of heterophile antibody response.

Discussion. Our findings indicate that sheep cells agglutinins and hemolysins appear in surprisingly high concentrations in the serum of patients during the acute stages of infectious mononucleosis. It is difficult to conceive of this phenomenon other than as an example of heterophile antibody production, perhaps analogous to the response which is known to exist in the acute phases of serum disease as a result of the injection of horse serum. Although the

* We are indebted to Mr. L. W. Slanetz, of the Department of Bacteriology, Yale University, for these cultures. The strain had been isolated from the gums of a patient several months previously and had been grown anaerobically during this time.

mechanisms involved are not clear, it is unlikely that the disease known as infectious mononucleosis should be the only condition in which this response is elicited without the *artificial* introduction into the body of a substance containing the heterophile antigen. Indeed, one exceptional case, which we have already reported above, would suggest that it may occasionally be demonstrated in other conditions. Nevertheless, in spite of the fact that the limits of the reaction which we have described have not been tested, it would seem to be of some diagnostic value. In a sense, however, it appears to be of more theoretical than practical interest. Theoretical interest centers about the fact that heterophile antibodies may be produced or enhanced during the course of human infectious disease, and in one disease in particular, in which the etiology has not been established. Furthermore, that two clinical entities with widely differing symptomatology, such as serum disease and infectious mononucleosis, would elicit the same type of serologic response is also worthy of interest. In serum disease the phenomenon of heterophile antibody production would seem to be more or less explainable, but in infectious mononucleosis we have no rational explanation. A possible one would be that these antibodies are produced as part of the direct immunologic response to infection by the unknown agent producing the disease. This theory will be difficult to prove, however, until the unknown infective agent is isolated and tested for the presence of the heterophile antigen. In the light of this approach, however, we have been unable to secure evidence that Vincent's fusiform bacilli are of etiologic import in this disease. On the other hand, it is also conceivable that the phenomenon which we have described is in the nature of an isoagglutinin response to the presence of an excess of *abnormal* cells either present in the blood or elsewhere. In any event, however, further work on this problem should logically be concentrated upon a search for the carrier of the heterophile antigen which probably lurks somewhere in the human body during the active stages of this disease.

Conclusions. 1. Heterophile antibodies, demonstrable in the form of sheep cell agglutinins, have been recorded in rather high concentrations in the active stages of 4 cases of infectious mononucleosis.

2. Apart from cases of serum disease, and one notable exception, we have failed to note this finding in a large series of cases representing a variety of clinical conditions, including cases of Vincent's angina, lymphatic leukemia and other blood dyscrasias.

3. There would seem to be two possible explanations for this finding: (1) that the unknown agent responsible for infectious mononucleosis contains the heterophile antigen; (2) that we are dealing with an example of isoagglutinin production elicited by abnormal cells, which are present either in the blood, or elsewhere, during active stages of the disease.

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MYELOID CELL HYPERPLASIA OF THE BONE MARROW IN AGRANULOCYTIC ANGINA.

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THE current concept of the bone marrow changes in so-called agranulocytic angina is that there exists, at least terminally, a more or less complete absence¹ of white cells of the granular (myeloid) series. This "granulocytic aplasia" concept has developed partly

on the basis of bone marrow studies indicating an apparently selective disappearance of the granular leukocytes and their progenitors and partly on the basis of analogy to established findings in certain other conditions, such as benzol poisoning, with its "selective" attack on formative tissues of the granular cells and blood platelets.

The possibility that such a concept may not be entirely well founded in fact, and may be misleading in implication, has come to mind from personal study of the bone marrow of 3 recent fatal cases. In 1 of these, reported below, the marrow of most of the bones examined contained "actively hemopoietic areas" filled with myelocytes, promyelocytes and myeloblasts, while the peripheral blood contained only 200 white blood cells per c.mm. (all lymphocytes). Similar, although less obvious, absence of myeloid white cell aplasia was found in the marrow of the other 2 cases. One of these died after months of illness characterized by repeated severe relapses and incomplete remissions. This patient's marrow, in most of the bones, was more nearly aplastic as regards granular series cells than any other marrow of such cases personally examined; but even this one showed numerous myeloblasts and a few myelocytes in the rib marrow, whereas her terminal white blood count was only 500 cells per c.mm. (all lymphocytes).

Necropsy was performed in these cases within 2 hours of death, and fresh bone marrow, spleen and lymph node smears were stained at once by the usual hematologic methods (Wright's, oxidase and cresyl blue). We believe this fresh smear technique to be a valuable hematologic adjunct to the study of the routine marrow sections of the pathologist.

While the majority opinion and findings of those who have reported on this disease would seem to favor the "aplastic" marrow hypothesis, there are several reports of myeloblastic and myelocytic hyperplasia on record,² to which the following is added:

Case Report. Mrs. L. S., a widow, aged 58 years, white, a native of Pennsylvania, was admitted to the care of Dr. F. C. Wood, University of Pennsylvania Hospital, on May 17, 1931. She had been well, except for occasional "neuritis" in her right arm and occasional sore throats, until May 15, when, following exposure to inclement weather, she developed increasing sore throat, fever and vomiting. Dr. Wood saw her on the morning of May 17 and made a leukocyte count which showed "less than 1000 leukocytes" per c.mm. and confirmed his clinical suspicion of "agranulocytic angina." Her past medical history included quinsy in childhood and several attacks of sore throat and vomiting in the past 2 years which seemed to her just like the present attack. In addition she had suffered from chronic discharging otitis media for some years, frequent headaches, acne and chronic constipation. She had "malaria" in adolescence and transient glycosuria (1911 to 1913). Intermittently for about 20 years the patient had noted recurring purpuric spots on her body, but had suffered no other hemorrhages. This purpura ceased spontaneously in 1925 and did not recur. There was no suggestion of hay fever, asthma, hives or drug idiosyncrasy obtainable in her past history.

The family history was interesting in that of 7 children born to the patient 3 had died in early infancy and 1 of these had purpuric blotches on the skin. Her parents died in old age and 4 siblings and 2 full-grown children were reported as living and well. One sister died of pulmonary tuberculosis.

Physical Findings. On admission to the hospital, examination showed high fever (101° F.), slight jaundice and the rather characteristic multiple ulcerations in the nasopharynx and tonsillar regions, each ulcer being covered by patchy grayish exudate and surrounded by a very thin zone of slight inflammatory reaction. There was slight general pharyngeal edema. The gums (edentulous) and tongue showed no ulceration. There was little or no cervical or other adenopathy. Spleen and liver were not palpably enlarged. Heart, lungs, abdominal organs, blood pressure, reflexes, etc., were all "normal." No petechiae, no peripheral edema and no vaginal or anal ulcerations were observed.

Laboratory Data. "Blood count (May 18, 1931): Red blood cells, 4,800,000 per c.mm.; leukocytes, 350; hemoglobin, 14 gms. (90 per cent.) Differential: 100 per cent lymphocytes. Red cells and platelets appear normal. Platelet count, 265,000 per c.mm. Bleeding and coagulation time tests, normal. Reticulocytes, 0.7 per cent."

May 18: Van den Bergh test: Direct, delayed; indirect, 1.2 units. Icterus index, 20.

May 18: Throat smear and culture: No Vincent's organisms found in the smear. Culture showed predominance of *Streptococcus viridans* and many hemolytic *Staphylococcus aureus* organisms.

May 18: Culture from right ear showed predominance of *Bacillus pyocyaneus*, moderate number of nonhemolytic *Staphylococcus albus* and many hemolytic streptococci.

May 18: Blood culture, subsequently reported "no growth after 10 days."

May 18: Urinalysis: Acid, 1025; light cloud of albumin, no sugar, many hyalin and light granular casts, a few leukocytes (?).

May 19: White blood count, 440 per c.mm. (all lymphocytes).

May 20: Blood count four hours before death: Red blood cells, 4,300,000 per c.mm.; white cells, 200; hemoglobin, 15.3 gms. (98 per cent.) Wright's stain and oxidase stain showed nothing but an occasional lymphocyte in many fields. Red cells and platelets normal.

Course and Treatment. Irregular fever continued, from 100° to 105° F.; tachycardia and dyspnea increased with mucus accumulation in the throat and trachea, dysphagia and terminal delirium. Three blood transfusions were administered and venesection was performed once. Liver extract, calcium gluconate, cod-liver oil, orange juice, oropharyngeal applications, oxygen tent and digitalis completed the list of therapeutic attempts. Roentgen ray therapy was not undertaken because the patient's condition was so grave that removal to the Roentgen ray department seemed inadvisable, especially in view of our experience indicating the fatuity of this form of treatment. The patient died at 3.40 P.M. on May 20, 1931.

Necropsy Findings. (Aut. 31-513, two hours after death; significant data as reported by Dr. Klinck.) "Chronic and acute ulcerative follicular tonsillitis." Sections from the tonsils showed "lumina of the crypts filled with necrotic material that is loaded with bacterial growths. The lymphoid cells are extremely plentiful and the bloodvessels congested. A few large mononuclears and a few plasma cells are mixed with the lymphocytes. No polymorphonuclears are present." There was found in some places "much necrosis" and in others "much fibrous tissue." The thyroid gland was normal except for "scattered collections of lymphoid cells" and some "increased interstitial fibrous tissue." The heart showed some "myo-

cardial degeneration; fibrosis of the left ventricle; fatty infiltration of the right ventricle." The lungs showed partial "atelectasis (lower right) and congestion;" the liver, "capsular perivascular sclerosis and congestion;" the spleen, "fibrosis and congestion" (weight, 140 gm.); the pancreas, "fatty atrophy; islet tissue plentiful;" the kidneys, "simple nephrosis;" the adrenals were "negative." The urinary bladder, gastrointestinal tract, aorta, lymph nodes, uterus and other organs all "negative," except the bone marrow, reported grossly as "moderately hyperplastic." The bone marrow sections were referred to Dr. Custer, whose special report is not yet published. However, he tells us that they show a considerable myeloblastic hyperplasia in the femur, tibia, ribs, etc. (Dr. Custer will include this case in a series of marrow studies soon to be published.)

Dr. Klinck made one other observation in this case which may be significant: Lymph nodes seemed scarce and hard to find. Postmortem culture of the splenic pulp was negative. The heart's blood showed a pure culture of *Bacillus coli communis*. *Pathologist's chief diagnosis:* Agranulocytic angina.

Study of Fresh Smear Preparations. Spreads were prepared on coverslips and glass slides from: (1) Blood from capillary pipette puncture of inferior vena cava, (2) heart's blood from right ventricle, (3) rib marrow, (4) sternal marrow, (5) vertebral marrow, (6) femoral marrow, (7) tibial marrow and (8) splenic pulp. These were immediately stained with Wright's and oxidase stain, and in some instances with cresyl blue.

I. Spreads of blood from the inferior vena cava showed red cells well distributed and of normal appearance (except that 1 normoblast was seen). Platelets were plentiful (in large clumps). The white cell count (estimated on the basis of observed ratio of 1 white cell to every 2000 red cells, with the assumption of 5,000,000 red cells per c.mm.) was about 2500 per c.mm. There were obviously more leukocytes in this blood than in that obtained 4 hours before death. Differential count of these cells was 74 per cent lymphocytes, 5 per cent monocytes and 21 per cent indeterminate mononuclear cells, some of which may have been lymphocytes, some possibly monocytes and several apparently young myelocytes (Wright's stain, 100 cells counted). The oxidase stain of the blood showed only 2 per cent granular mononucleated cells (*i. e.*, myelocytes or monocytes) and 98 per cent nongranular (lymphocytes). The cresyl blue preparation showed 2 per cent reticulocytes.

II. Heart's blood spreads were essentially similar to the above except that no oxidase-positive cells were found. One endothelial macrophage was seen which contained remnants of an engulfed cell (lymphocyte?).

III. Rib marrow smears (Wright's) appeared normal in cellular content except for (*a*) the complete absence of polymorphonuclear neutrophils and eosinophils and (*b*) the presence of abnormal numbers of young myelocytes with pale nuclei and many neutrophilic granules in the cytoplasm. Aside from the fat cells, which were present in no excess, the hemopoietic tissue was composed of:

(a) Myelocytes and promyelocytes, about 20 per cent. (Fig. 1.) (b) Lymphocytes, about 10 per cent. (c) Unidentified mononuclear cells of varying sizes (larger than the obvious lymphocytes), with pale nuclei and nongranular or finely granular cytoplasm (either myeloblasts, monocytes or lymphoblasts; probably myeloblasts), about 20 per cent. (d) Red blood cells, including numerous normoblasts and a few macronormoblasts, about 50 per cent. (e) An occasional typical megakaryocyte. (f) A few gigantic cells, each with a large fairly well-defined nucleus (containing nucleoli) and a wide grayish blue finely mottled cytoplasm containing vacuoles and marginal inclusion bodies, which were interpreted as hypertrophied reticulo-endothelial cells. (Figs. 1 and 2.)

Oxidase preparations of the rib marrow showed an essentially similar picture. A differential count of 500 white cells in scattered areas showed 42 per cent granular mononuclear cells (presumably myelocytes) and 58 per cent nongranular cells (lymphocytes, myeloblasts and possibly monocytes). Fifty normoblasts were seen while counting 500 white cells. The gigantic cells previously described from Wright's stain preparation appeared to be nongranular in the oxidase stain.

IV. Sternal and vertebral marrow spreads all showed a less definite picture of myeloid white cell activity, presumably because of osteosclerosis which rendered the smear method unsatisfactory.

V. Femoral marrow spreads were very similar to those of the rib marrow, except for a greater proportion of red cell elements in comparison to white cells. (Fig. 2.)

VI. Tibial marrow smears (from the point selected at necropsy) were entirely fatty.

VII. Splenic pulp smears (Fig. 3) showed nothing but profusion of lymphocytes and lymphoblasts and a few red cells (Wright's stain). These cells were all nongranular in the oxidase preparation.

Discussion. The presence of bone marrow progenitors of the granular series of blood cells in this case was not the result of Roentgen ray stimulation³ because this patient did not receive any such treatment. That these cells were myelocytes and myeloblasts (rather than monocytes) seems evident, although no supravital technique was employed in the staining. Death in this case was due to the disease itself rather than to some intercurrent condition which might be conceived as cutting short the course before the bone marrow lesions had developed to their final stage.⁴

The general leukopenia of this disease involves not only the granulocytes proper but usually the lymphocytes and monocytes as well.⁵ The absolute lymphopenia may be considerable even though the relative percentage is greatly increased. Other elements of the blood are rarely affected. The case here described, together with others referred to, make it clear that, at least occasionally, death may occur in uncomplicated "agranulocytic angina" with a

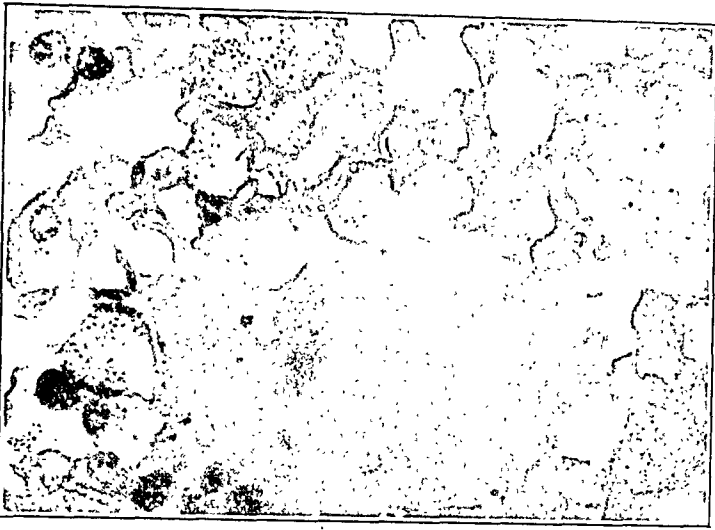


FIG. 1.—Rib marrow (Wright's stain), showing myelocytes, myeloblasts (here appearing very pale), a few lymphocytes, red cells and a large reticuloendothelial cell in the center. ($\times 644$.)



FIG. 2.—Femoral marrow (high magnification), showing a gigantic reticuloendothelial cell, several myelocytes and red cells. ($\times 1472$.)

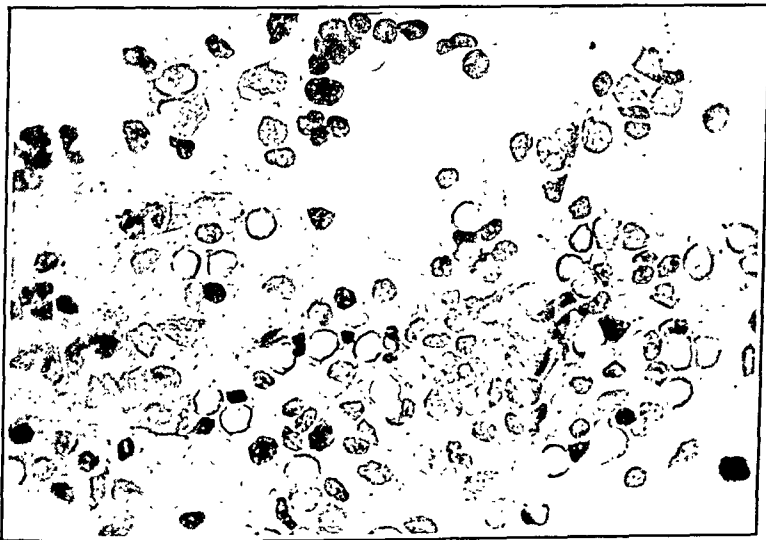
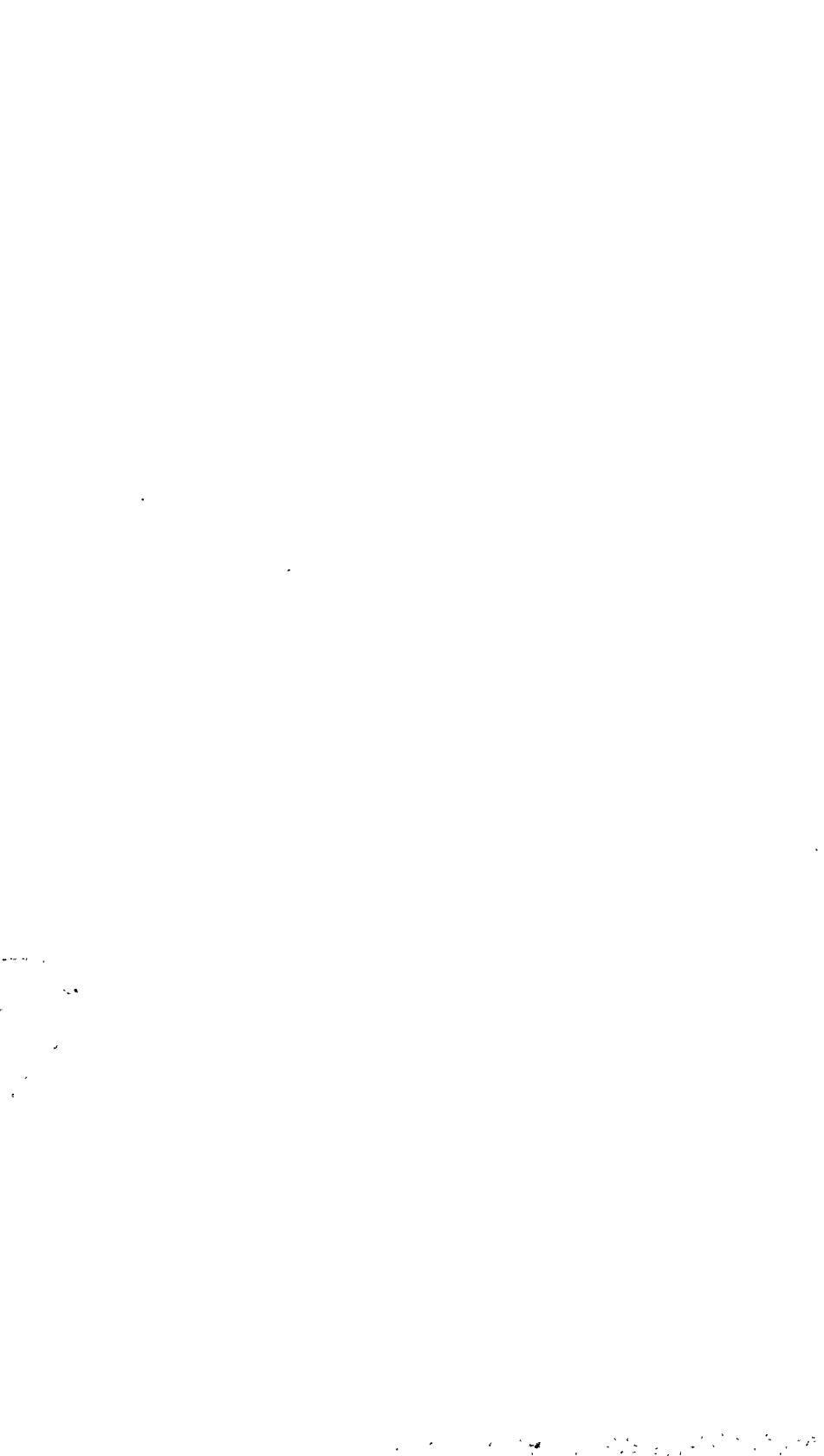


FIG. 3.—Splenic pulp smear (low magnification), showing the small dark lymphocytes; the larger pale, lymphoblasts and monocytes, and red cells (Wright's stain). ($\times 368$.)



profound peripheral leukopenia, while at the same time the leukopoietic centers for granulocytes and lymphocytes (and monocytes?) are well supplied with parent cells. The fact that this state of affairs may exist, even in an occasional case, serves to emphasize the apparent inadequacy of the general "granulocytic aplasia" hypothesis.

It would seem more probable here that a "maturation factor" is at work; either arresting development of white cells in their formative centers or producing degenerative changes in them before sufficient development for normal migration into the bloodstream, or possibly a combination of both factors. This hypothetical factor would conceivably check the granular series of blood cells at the myeloblast-myelocyte stage in the bone marrow and the lymphocyte series at or near the lymphoblast stage in the spleen and lymph nodes. Viewed from this standpoint, the analogies to pernicious anemia are obvious. Pernicious anemia too has remissions and relapses. It too is, as yet, an "idiopathic" disorder with probably a "constitutional" background of prime importance. It too may be closely mimicked by other disorders. Its relapses are characterized by megaloblastic hyperplasia of the bone marrow caused, according to the modern view (Minot), by some maturation-inhibiting factor directed against the red cell series. This concept, transposed to the white cell disturbances of "agranulocytic angina," would in no way deny the probability of a terminal, secondary destruction (or "aplasia") of bone marrow, spleen and lymph node cells in many instances, such as is known to occur in the bone marrow at the end ("aplastic") stage of untreated or poorly treated pernicious anemia.

For these reasons, and with apologies for adding another variant designation to this already much-named disease, the term *pernicious leukopenia* is suggested.

It is, of course, not contended here that anything approximating proof of a maturation factor in the disease has been adduced. The entire problem of the mechanism of leukocytosis and leukopenia in relation to the leukopoietic organs themselves is unsolved. Aleukemic and leukopenic forms and phases of leukemia and intermittent purpura hemorrhagica, as well as pernicious anemia, all present certain interesting analogies to the disease under consideration.

Summary. 1. Myelocytes and myeloblasts were found in the bone marrow at necropsy in more than normal numbers in a case of typical "agranulocytic angina" whose antemortem blood count was 200 white cells per c.mm. (all lymphocytes), *i. e.*, a marked absolute reduction of lymphocytes and absence of all other white cells.

2. Based on this and similar cases recorded in the literature, objection is raised to the current hypothesis of "granulocytic aplasia" as constituting the "primary" pathologic mechanism of

the disease, and in its place an hypothesis of "maturation arrest" is proposed for consideration and future study.

3. Inasmuch as there is an absolute reduction of lymphocytes in the blood stream as well as of neutrophils and on account of certain analogies with pernicious anemia, designation such as *pernicious leukopenia* is suggested as preferable to the more widely used names for this disease.

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THE RESPONSE OF THE RETICULOCYTES TO IRON.

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THE response of the reticulocytes in pernicious anemia to effective material gives information regarding the potency of the substance administered, the rate of rise of the red blood cells and the

desirable dose for a given case. It aids in determining whether the patient has difficulty in absorbing or utilizing the product when given orally and can thus lead to the advantageous use of a product given parenterally. Because this reaction has been shown to be of distinct value in pernicious anemia a study is being made of the response of the reticulocytes to iron in anemias that can be affected by this element.* Some of the information so far obtained from the oral administration of iron is presented here.

Data concerning positive reticulocyte responses have been obtained for over 100 cases, but only complete data for 66 cases and partial data for 20 additional cases first treated with maximal amounts of iron are for consideration at present. Those patients who have responded distinctly, but to varying degrees, to iron therapy include cases of anemia due to chronic blood loss with and without recent acute exacerbations, dietary defects, gastrointestinal disorders and pregnancy. Cases of ill-defined anemia, especially in women, and cases of idiopathic hypochromic anemia (simple achlorhydric anemia) are also included. In many cases more than one cause for anemia was present, including such complications as infections.

In cases of pernicious anemia without serious complications treated with maximal amounts of liver or potent substitute the height of the reticulocyte rise is inversely proportional to the level of the red blood cells directly before treatment. There is also a relation of the same sort between the hemoglobin level and the numbers of reticulocytes at the peak of their rise. Similar but less exact relationships exist for the anemias responding to iron, as is illustrated in Figs. 1 and 2. Each case was treated daily with from 3 to 4 gm. of ferrous carbonate or 4 to 6 gm. of iron and ammonium citrate. In all instances the hemoglobin and red blood cells increased to normal or to a very considerable degree. The patients were all adults, except for 2 children under 5 years of age, who had distinctly high reticulocyte responses. It is possible, owing to the character of the bone marrow in youth, that under comparable circumstances a relatively greater response of reticulocytes will occur in children than in adults.

Infections and other complications, such as pronounced arteriosclerosis, appear to hinder the action of iron just as they hinder the effect of potent material in pernicious anemia. Such conditions in the cases responding to iron appear to have played only a slight rôle in causing a more widely spread distribution of maximal reticulocyte rises than in comparable cases of pernicious anemia. However, the incidence of complications, especially infections, among the 16 cases with the lower reticulocyte rises for a given

* The iron salts administered were not purified, but were ones commonly prescribed which are usually contaminated with small amounts of copper and sometimes with other elements.

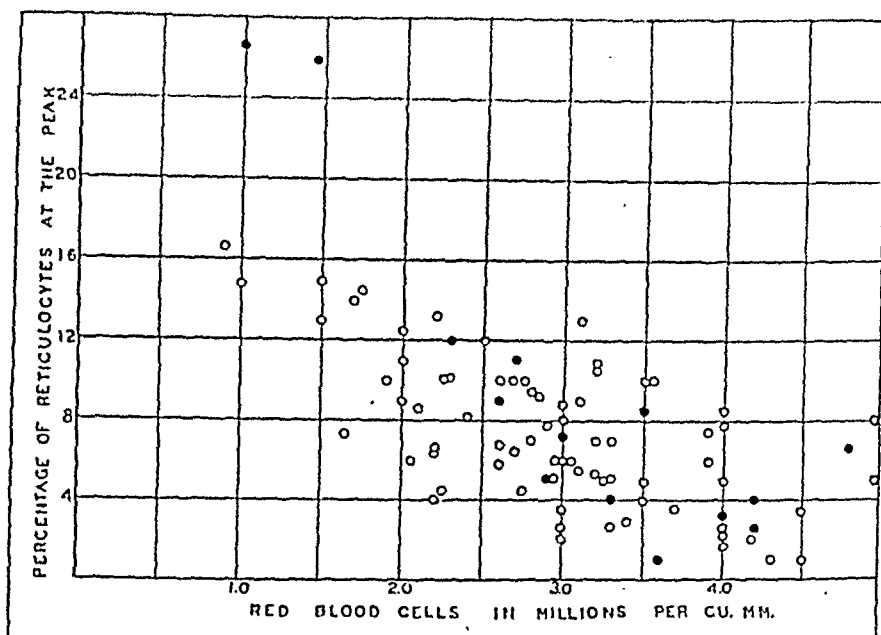


FIG. 1.—The relationship between the level of the red blood cells before treatment with iron and the percentage of reticulocytes at the peak of their rise. Each dot represents 1 case. The black dots represent uncomplicated cases of anemia due to chronic blood loss or to chronic dietary deficiency which manufactured blood in response to iron feeding at a maximal rate.

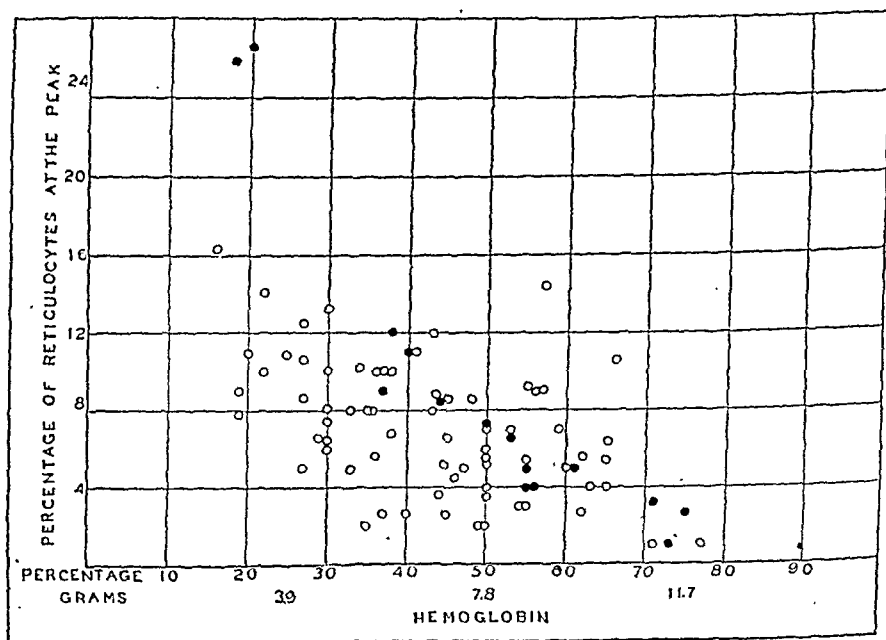


FIG. 2.—The relationship between the level of the hemoglobin before treatment with iron and the percentage of reticulocytes at the peak of their rise. Significance of dots as in Fig. 1.

red blood cell level below 3 million per c.mm. was four times as great as for the other 33 cases with comparable numbers of corpuscles. A similar state of affairs exists for a comparison with the hemoglobin level. When data were studied for uncomplicated cases of anemia due to chronic blood loss or chronic dietary deficiency (black dots, Figs. 1 and 2) responding to iron with maximal production of hemoglobin and red blood cells, it was found that the number of reticulocytes at the peak of their rise could be correlated more closely with the hemoglobin than with the red blood cell level. This becomes particularly evident in cases with distinctly low hemoglobin values and essentially normal red blood cell counts, so that distinct rises of reticulocytes occur in response to iron with red blood cell levels at which in pernicious anemia insignificant reticulocyte increases take place. Thus, in the types of anemia under consideration for a given red cell level above approximately 2.5 million per c.mm., a greater rise of reticulocytes occurs in response to maximal doses of iron than in pernicious anemia in response to adequate amounts of liver and allied products. It is rare to have uncomplicated cases of anemia responding to iron with red blood cells below 1.5 million per c.mm., so that a comparison at very low red blood cell levels is difficult to evaluate. However, with red blood cell levels below approximately 2.5 million per c.mm. the rise of reticulocytes in response to adequate therapy appears to be somewhat similar in the different types of anemia. On the contrary, in pernicious anemia with hemoglobin levels below about 10 gm. (64.1 per cent)* the rise of reticulocytes in response to adequate treatment is progressively greater than in "secondary" anemia. Below the level of about 5 gm. (32 per cent) hemoglobin the increase of reticulocytes in pernicious anemia is on the average at least double that which occurs in "secondary" anemia. This state of affairs suggested that in order to evaluate fully the reticulocyte response to iron, especially if the red blood cells are above 2.5 million per c.mm., there should be considered both the hemoglobin and red blood cell level. Data at hand suggest that relationships exist between the reticulocyte response and the corpuscular volume, hematocrit and state of the bone marrow, as told by the numbers and characters of the white blood cells; but these matters will not be discussed here.

An unselected series of 66 cases was divided into two groups according to whether the color index was below or above 0.66. (Fig. 3.) The mean red blood cell counts of each group were essentially the same, namely, 3.15 and 2.95 million per c.mm., respectively. The first group of 32 cases had a mean hemoglobin of

* Grams of hemoglobin indicate grams per 100 cc. of blood determined by the Sahli hemoglobinometer, allowing that 15.6 gm. of hemoglobin are equivalent to 21 volumes per cent oxygen capacity as determined by the van Slyke method, or 100 per cent hemoglobin.

5.3 gm. (34.2 per cent) and a mean color index of 0.54; the second group of 34 cases had a mean hemoglobin of 7.4 gm. (47.3 per cent) and a mean color index of 0.8. A plot of the daily average reticulocyte count after iron therapy was begun shows that the curve for the cases with the lower mean hemoglobin and color index rises faster and one-fifth again higher than for the cases with the higher mean hemoglobin and color index. A further survey of the relationships between the reticulocyte response to iron and the color index, red blood cell and hemoglobin levels is presented in Fig. 4.

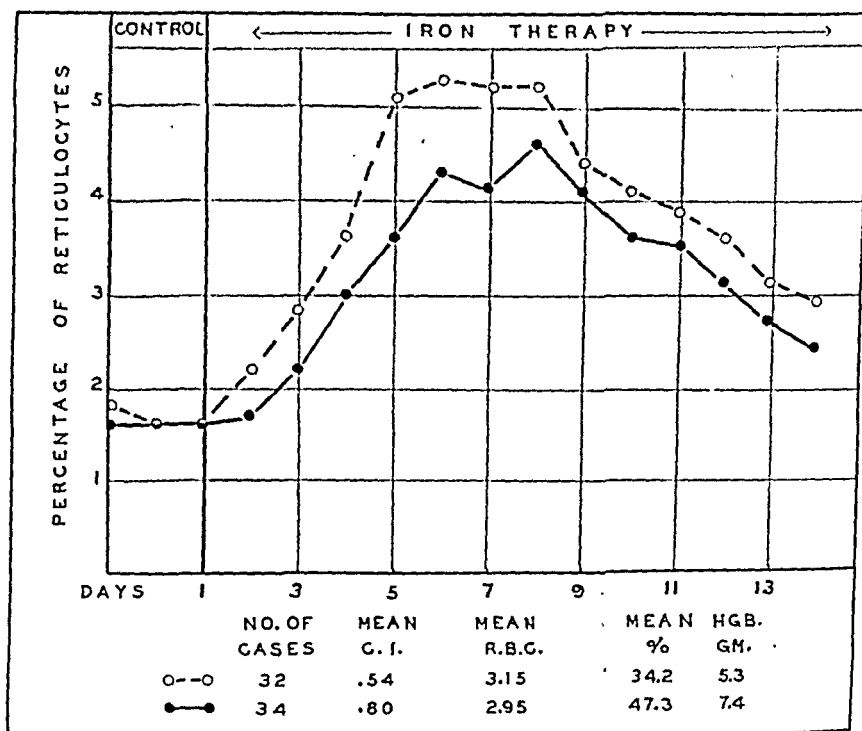


FIG. 3.—The mean response of the reticulocytes to iron in two groups of cases selected according to whether their color index was above or below 0.66.

As the figure shows, there is a similar relationship between the reticulocyte response and the color index in 26 of these 66 cases selected with approximately equal red blood cell counts between 2.5 and 3.5 million per c.mm. and divided according to whether the hemoglobin was above or below 6.9 gm. (44 per cent). However, when 18 cases were selected with approximately equal hemoglobin values averaging 6.4 gm. (41 per cent) and divided according to whether the red blood cells were above or below 3 million per c.mm., then a reverse state of affairs occurred so far as color index is concerned. The cases with the lower red blood cell counts

(average 2.61 million per c.mm.) had an average color index of 0.79 and those with the higher red cell counts (average, 3.83 million per c.mm.) had an average color index of 0.54, but the reticulocytes increase more in the former than in the latter group. The data show, of course, that cases may have the same color index, with the reticulocytes rising to very different numbers, dependent on the red blood cell and hemoglobin level.

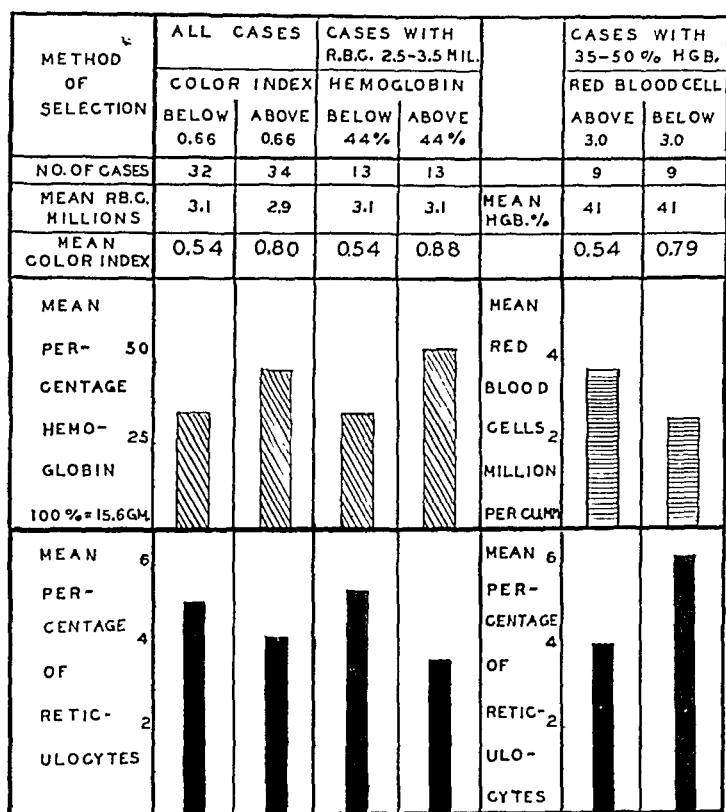


FIG. 4.—Mean maximal reticulocyte responses to iron correlated with color index, hemoglobin and red blood cell level.

It thus appears that for a given red blood cell level the reticulocyte response to maximal doses of iron will be greater the lower the hemoglobin, and the increase of reticulocytes will be greater for a given hemoglobin level the lower the red blood cell count. Although for pernicious anemia the distinctions are not so great, it appears from a special study of 58 uncomplicated cases that there is in this disease a tendency for the reticulocyte response at any given red blood cell or hemoglobin level to be slightly higher in direct proportion to the color index.

A case of anemia responding to iron may be considered more severe the lower both the hemoglobin and red blood cell level, and the patient with pernicious anemia with a rising color index is

relapsing. The height of the reticulocyte response to iron will be greater the lower both the hemoglobin and the red blood cells, and greater in pernicious anemia the lower the red blood cell level and the higher the color index at a given red blood cell level. This perhaps is because in pernicious anemia the need is primarily for cell production and apparently in anemias responding to iron it is particularly for hemoglobin production, although neither factor is

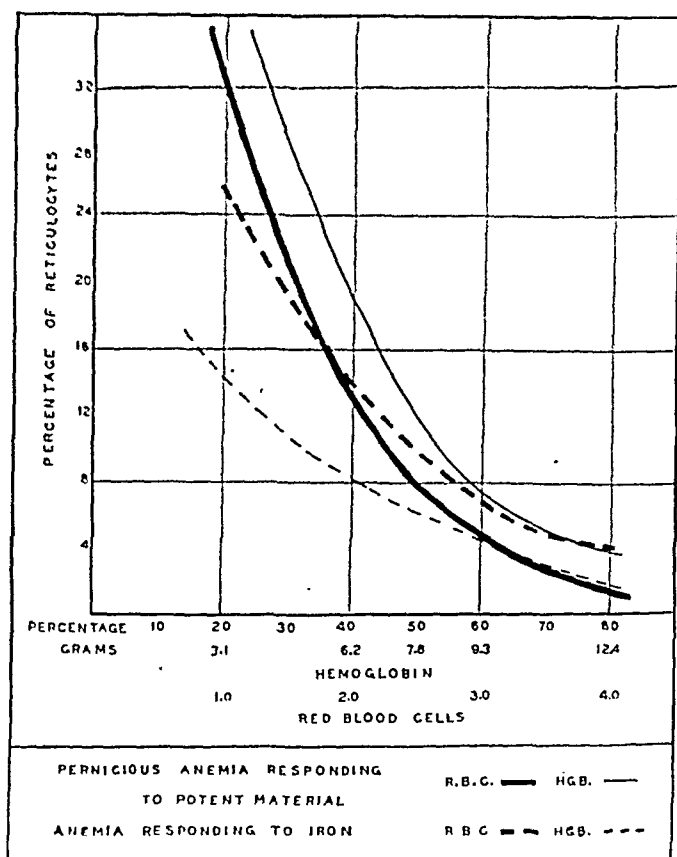


FIG. 5.—The trend of the reticulocytes at the peak of their rise in cases of pernicious anemia responding to potent material and in cases of anemia responding to iron. Red blood cell levels in millions per cubic millimeters and hemoglobin levels before treatment recorded as abscissæ.

independent of the other. Fig. 5 shows graphically in a broad way the relationships between hemoglobin and red blood cell levels and the percentage of reticulocytes at the peak of their rise in response to adequate therapy for pernicious anemia and for anemias responding to iron.

The divergent types of cases responding to iron play some rôle in the degree of the reticulocyte response. In evaluating the

response the exact type of case with its altered pathologic physiology should be considered, although the red blood cell and hemoglobin level are the most important factors in determining the level to which the reticulocytes will rise. Abnormality of the gastrointestinal tract and its contents can play an important rôle in the production of anemia. Castle and his associates¹ have shown the great etiologic significance of the lack of an undetermined factor in the stomach of pernicious anemia. Achlorhydria, especially when persistent after the administration of histamin, or defects associated with it, very probably enhances the development of many cases of anemia. Probably achlorhydria or defects which often accompany it favor the malabsorption or improper utilization of substances necessary for the maintenance of normal blood and other normal states.² Thus the response of the reticulocytes to iron in relation to achlorhydria has been considered. Apparently in cases with similar red blood cell and hemoglobin levels there is a definite tendency for those with achlorhydria to have a reticulocyte response to iron of less magnitude than cases with free hydrochloric acid in the gastric contents. Furthermore, data presented in Table 1 suggest that the former cases on the average increase the concentration of their erythrocytes and hemoglobin in response to iron more slowly than the latter, and this has been found true, especially when relatively small doses of iron are given. This is in accord with observations made by Witts,^{3,4} who notes that cases of chronic microcytic anemia with achlorhydria respond to iron more slowly than cases of chlorosis and anemia due to blood loss with free hydrochloric acid in the gastric contents. These observations illustrate that the response of the blood elements to iron depend in a measure on the exact type of the anemic patient who is treated.

TABLE 1.—A COMPARISON OF THE RESPONSE TO IRON IN CASES OF ANEMIA WITH AND WITHOUT FREE HYDROCHLORIC ACID IN THE GASTRIC CONTENTS.

	Free HCl.	No free HCl (histamin subcutaneously).
Number of cases	24	24
Mean red blood cells before treatment, millions per c.mm.	3.1	3.2
Mean hemoglobin before treatment, per cent	42	42
Mean reticulocytes at peak of response, per cent	7.1	5.2
Mean hemoglobin increase per day, per cent	1.18	0.85
Mean red blood cell increase per day, per c.mm.	60,000	53,000

For the sake of clarity cases are selected so that the number of red blood cells and percentage of hemoglobin before treatment are similar in the two series. However, the cases which have been discarded show a difference in their response to iron similar to that shown in this table, in spite of the fact that the cases without free hydrochloric acid had on the average a much lower color index than the cases with free hydrochloric acid. The mean red blood cell and hemoglobin increase per day is determined in nearly all instances by averaging the total increases during the first 28 days following commencement of treatment. One hundred per cent hemoglobin is equivalent to 15.6 gm. per 100 cc. of blood.

The rate of manufacture of hemoglobin in cases responding to optimal amounts of iron and with an initial hemoglobin level of less than 6.2 gm. (40 per cent) can be predicted approximately from the level of the reticulocytes at the peak of their rise. This is illustrated by the data for 24 unselected cases presented in Fig. 6. The hemoglobin increased on the average 5.3 gm. (34 per cent) in 28 days. There is in general a direct relationship between the height of the reticulocyte rise and the rate of increase of hemoglobin.

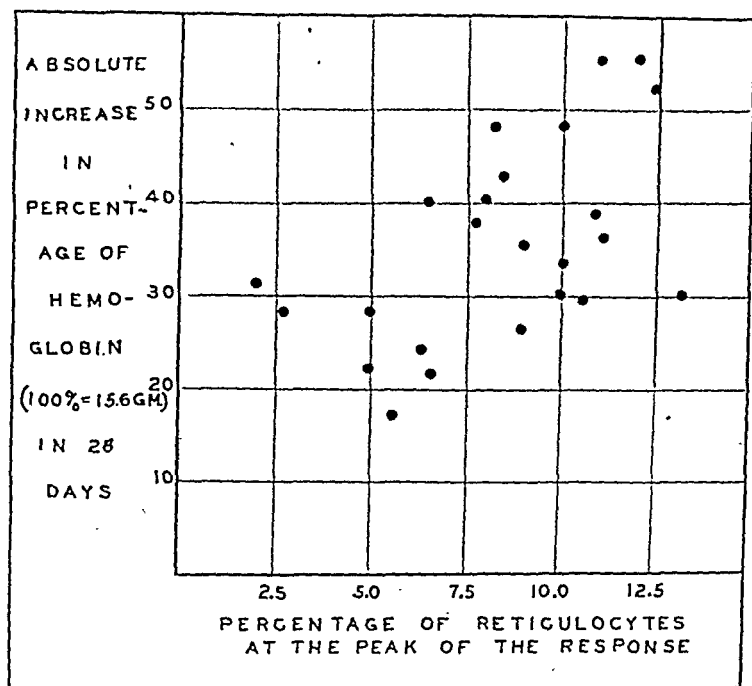


FIG. 6.—The direct relationship between the height of the reticulocyte rise and the rate of hemoglobin increase in 24 cases of anemia responding to optimal amounts of iron with an initial hemoglobin level of less than 6.2 gm. (40 per cent).

The character of the response of the reticulocytes as determined by the curve yielded from plotting the data obtained from daily reticulocyte counts may have biologic significance and may give information concerning pathologic physiology, treatment and prognosis. Fig. 7 gives examples of the course taken by the reticulocytes in response to maximal amounts of potent material for pernicious anemia and in response to maximal amounts of iron in anemia chiefly due to chronic blood loss. There is a tendency for cases responding to iron given daily by mouth to develop a reticulocyte response sooner than cases of pernicious anemia treated in a similar manner by potent material. The reticulocyte response to

iron occurs sooner in some cases than in others. There is also a distinct tendency of the curves for reticulocytes responding to iron to have more often flatter tops than those for pernicious anemia, so that frequently the reticulocytes occur in approximately the same numbers for 4 days at the height of their rise. A definite decrease for 1 or 2 days after a rapid rise to a maximum followed by an increase for 1 to 3 days of about equal magnitude to the former maximum occasionally occurs. Prolonged parabola-shaped curves,

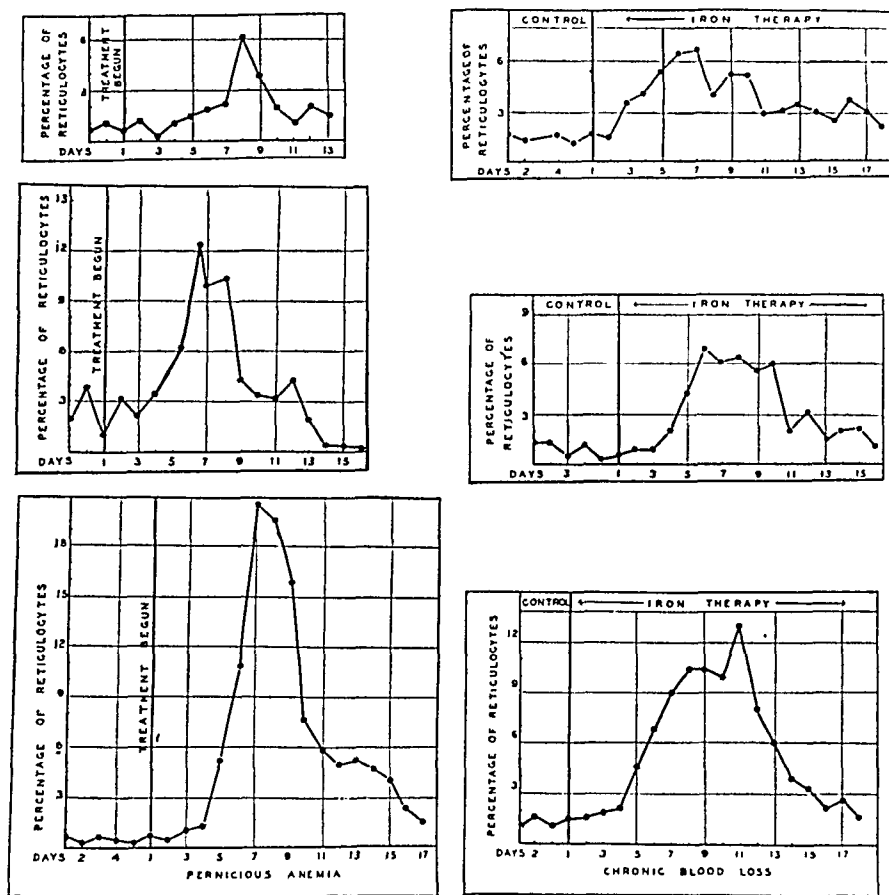


FIG. 7.—Examples of the course taken by the reticulocytes. The response to maximal amounts of potent liver preparations in 3 cases of pernicious anemia and to 6 gm. of iron and ammonium citrate fed daily in 3 cases of anemia chiefly due to chronic blood loss.

especially in cases with very low color indices and with approximately a normal number of red blood cells are not unusual and resemble the curves seen at times in pernicious anemia treated with suboptimal amounts of potent material. The duration of the reticulocyte response to iron usually lasts, however, about as long as in adequately treated cases of pernicious anemia, which is in the vicinity of 12 days. It is probable that more accurate comparisons of reticulocyte responses for their prognostic significance, relation to dose of potent material and the like could be made if considera-

tion was given to the total number of reticulocytes produced during the period of their response. That is to say, a response with a quick rise and fall of reticulocytes may not indicate as satisfactory a state of affairs, other things being equal, as a response with a sustained rise of reticulocytes which did not reach as high a level as in the former case. This has been referred to previously for pernicious anemia.⁵ However, for practical purposes a consideration of the percentage or absolute number of reticulocytes at the peak of their rise gives useful information.

The study of the effects of iron include observations not only on the types of cases in which it may and may not be useful in promoting blood regeneration but also upon other matters such as dosage. No response to iron may be expected when anemia is primarily due, among other conditions, to infection, nephritis, scurvy, myxedema, true bone-marrow aplasia, metaplasia or megaloblastic hyperplasia as occurs in pernicious anemia. However, it must not be forgotten that some response to iron may occur in patients with such conditions because there may also exist anemia due to a condition that can respond to iron. The chief sorts of anemia that can respond to iron are those due to chronic blood loss, various sorts of dietary deficiency and altered gastrointestinal function, pregnancy and various types of chronic anemia of microcytic type without well-recognized cause, which are especially common in women.

The dosage of iron has been studied in various ways, especially by reticulocyte responses to varying amounts of iron in the same case. Although it is evident that small amounts of iron may accomplish distinctly beneficial results, it is also evident that large doses can accomplish the desired results when small doses cannot do so. This is especially true for cases of idiopathic hypochromic anemia (simple achlorhydric anemia) in which condition many, if not all, such patients must continue to take iron indefinitely after it has restored the blood to normal or else relapse ensues.

There are many ways of studying the multiple aspects of iron therapy. However, among other methods the course taken by the reticulocytes will be found serviceable, but such information must not be used alone, for the problems concerning anemia will be solved by bedside observations expanded in the laboratory. The observations must be made with strict accuracy and with the recognition that the scientific problem is associated with an appeal of immediate human interest.

Summary. A study is presented concerning *positive* reticulocyte responses to the daily oral administration of iron in maximal amounts to patients with anemia especially due to chronic blood loss, dietary defects, gastrointestinal disorders and pregnancy and to patients with chronic microcytic anemia of obscure origin.

The height of the reticulocyte rise is in general inversely proportional to the level of the red blood cells and hemoglobin directly

before treatment, but the relationships are less exact for the anemias responding to iron than for pernicious anemia in response to liver or potent substitute.

Infections and other complications hinder the action of iron similar to the way in which they hinder the effect of potent material for pernicious anemia.

Distinct rises of reticulocytes occur with low hemoglobin values in response to iron when the red blood cell level is one at which in pernicious anemia insignificant reticulocyte increases take place. With red blood cells above 2.5 million per c.mm. a greater rise of reticulocytes occurs in response to maximal amounts of iron than in pernicious anemia in response to adequate amounts of potent material; but when the red blood cells are below this number the reticulocytes rise in response to adequate therapy to a somewhat similar number in the different types of anemia. On the contrary, in pernicious anemia as the hemoglobin level decreases below about 10 gm. per 100 cc. of blood the rise of the reticulocytes becomes progressively greater than in "secondary" anemia, so that it is at least double when the hemoglobin is less than about 5 gm. per 100 cc. of blood.

Both the hemoglobin and red blood cell levels must be considered in evaluating the reticulocyte response to iron. For a given red blood cell level the reticulocytes will increase more the lower the hemoglobin and the increase of reticulocytes will be greater at a given hemoglobin level the lower the red blood cell count.

The exact type of case responding to iron plays a rôle in the degree of reticulocyte response. Cases with achlorhydria tend to have a slightly smaller response and to manufacture blood more slowly than comparable cases with free hydrochloric acid in their stomach contents.

The character of the curves yielded from plotting data obtained from daily reticulocyte counts in response to iron tend to differ somewhat from those obtained for pernicious anemia in response to liver or potent substitutes.

NOTE.—It is a pleasure to acknowledge our indebtedness to Dr. Chester S. Keefer and Dr. Leon G. Zerfas for supplying us with data on some cases.

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REVIEWS.

THE INGENIOUS DR. FRANKLIN. Selected Scientific Letters of Benjamin Franklin. Edited by Nathan G. Goodman. Pp. 244; illustrated. Philadelphia: University of Pennsylvania Press, 1931. Price, \$3.00.

WITH the passage of time no 18th century American figure looms larger than that of the great printer-philosopher-scientist-diplomat. The perennial interest in this fascinating personality is manifested, to be sure, in such works as "The True Benjamin Franklin," "The Medical Side of Benjamin Franklin," "The Many-sided Franklin," and so on; but with the exception of "My Dear Girl" (a charming series of letters to two young ladies in London), his own writings must still be sought in "ponderous volumes of collected works." The present series of 57 letters on a wide range of his scientific investigations and speculations is a desirable addition to Frankliniana, especially when presented in such an attractive format. While excellent productions are perhaps only what we have come to expect from the best University Presses, we should not fail to appreciate how much the present revival in artistic bookmaking owes to these altruistic, nonprofit-making producers.

The letters selected, some of which have never been published before, include such timely topics as Daylight Saving, Electrical Treatment for Paralysis, Bifocals, Smallpox and Cancer, Cause of Colds, Sunspots, Toads Found in Stone and 5 on aerial navigation. They give ample evidence of the author's insatiable, constructive curiosity and the vitality of his mental processes, while his philosophic goal is indicated by such characteristic queries as "What signifies philosophy that does not apply to some use?" A list of additional letters and papers of general interest completes this highly entertaining volume.

E. K.

HARPER'S MEDICAL MONOGRAPHS, VOLS. I AND II. TREATMENT OF INJURY. By CLAY RAY MURRAY, M.D., F.A.C.S., Assistant Professor of Surgery, College of Physicians and Surgeons, Columbia University. Pp. 412; 196 drawings by the author. New York: Harper & Bros., 1931. Price, \$5.00, 2 vols.

THIS seventh member of Harper's Medical Monograph series is a worthy fellow of its predecessors. Dr. Murray, in his effort to show the general practitioner "what to do" with injury, has written one

of the most practical manuals on traumatic surgery available in the English language.

His material is divided into five parts. Part I treats of injuries to soft parts. He gives full consideration to the too often neglected treatment of muscle, tendon, and bursal injuries, abdominal and chest injuries, and burns. In Part II he comes into his own in his treatise on fractures, except those of the spine and skull. The section is introduced by an excellent discussion of the general principles of fracture treatment, and is followed by a detailed description of individual fractures, illustrated by ample line drawings. The reader is taught and shown the various types of deformity which may occur at the same fracture site, and the author thereby emphasizes the importance of adapting the treatment to suit the individual needs of the fracture and patient. This portion of the book easily ranks as the equal of many larger works on fracture treatment.

Part III deals with dislocation and Part IV with spinal and cranial injury. The fifth part treats of miscellaneous trauma and includes joint injury, and foreign body wounds.

The publishers have recommended the work as particularly adapted to the needs of the general practitioner. It is more than that. It is a work which may be commended to all (surgeons, medical students, industrial physicians, etc.) who wish to easily learn the approved methods of the treatment of injury. Dr. Murray's lucid style makes an easy reading text, and the convenient size and binding of the volumes combine to make the set one well-worth having.

L. F.

PHYSICAL DIAGNOSIS. By WARREN P. ELMER, B.S., M.D., Associate Professor of Clinical Medicine, Washington University, St. Louis, and W. D. ROSE, M.D., Late Associate Professor of Medicine University of Arkansas, Little Rock. Pp. 903; 337 illustrations. Sixth Edition. St. Louis: The C. V. Mosby Company, 1930. Price, \$10.00.

DR. ELMER, in revising Dr. Rose's work, has not only largely rewritten the book, but has also largely rearranged the material. So, in Part I, devoted to the technique of physical examination and normal physical findings, each diagnostic procedure is described for the whole body before taking up the next: *e. g.*, the inspection of the whole body is discussed before palpation is introduced. The book is primarily intended for teaching physical diagnosis to medical students, and for this purpose the book is altogether adequate. There is, however, no specific mention of the physical signs that may arise from foreign bodies in the air passages. A better grade of paper has served to improve the illustration over those of previous editions.

R. K.

CHEMISTRY FOR NURSES. By HARRY C. BIDDLE, A.M., Instructor in Chemistry, School of Nursing, Western Reserve University. Pp. 336; 74 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, \$2.75.

THIS book, arranged as a textbook and laboratory manual, contains the important material that may be covered in the 45-hour period as recommended by the National League of Nursing Education.

Each chapter begins with a topical outline, and a series of questions that are bound to arise regarding the chemistry facts in the practice of nursing. These questions having aroused the interest of the student are answered in the subject matter following. Review questions and suggestions for reports and charts that may be used by those students able to go further, complete the lesson.

The laboratory exercises, both simple and practical with a few blank pages for personal notes, follow each lesson. An appendix containing miscellaneous chemistry facts, important to a nurse, and an index complete this text that is without doubt the best text in chemistry that we know of for nurses.

M. S.

A MANUAL OF PRACTICAL VERTEBRATE MORPHOLOGY. By J. T. SAUNDERS and S. M. MANTON. Pp. 220; 43 illustrations. New York: Oxford University Press, 1931. Price, \$5.00.

THIS book is essentially a text and laboratory guide for beginners in comparative anatomy. Directions are given for dissection of various lower vertebrates and the pigeon, as well as the brain of a sheep. The figures accompanying these directions are so arranged that they may be colored. In the last three chapters the comparative anatomy of the vertebrate skull, teeth and the osseous system are considered. Investigators having need for a handy reference to the anatomy of the lower vertebrates will find this book of considerable value.

H. R.

THE INFANT WELFARE MOVEMENT IN THE EIGHTEENTH CENTURY. By ERNEST CAULFIELD, M.S., M.D. With a Foreword by GEORGE FREDERIC STILL, M.A., M.D. (CANTAB.), HON. LL.D. (EDIN.), F.R.C.P. (LONDON). Pp. 203; 8 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, \$2.00.

CHILDREN are being well treated to-day from the medical history standpoint. No sooner had Ruhräh's Pediatrics of the Past become well settled in its proper niche than Still's History of Pediatrics arrived. This barely off the press when the present volume presents another aspect of the subject in an entertaining and instructive

manner. The rise of the infant welfare movement in England is especially well portrayed, whole chapters being given to Coram and the Foundling Hospital, William Cadogan, Hanway and George Armstrong (the author's special favorite). While the book does not pose as and should not be taken for a complete record of the movement, it has the stuff of real history and is a contribution well worth while.

E. K.

LEHRBUCH DER ALLGEMEINEN PHYSIOLOGIE. By E. GELLHORN, PH.D., M.D., a. o. Professor of Physiology, Halle and Associate Professor of Physiology, University of Oregon. (With the collaboration of L. ASCHER, Bern, W. VON BUDDENBROCK, Kiel, C. OPPENHEIMER, Berlin, and J. SPEK, Heidelberg.) Pp. 741; 126 illustrations. Leipzig: Georg Thieme, 1931. Price, M. 49.50.

THE present volume covers, in what is on the whole a thorough and authoritative manner, the various subjects commonly included under the term "General Physiology." It comprises sections of 234 pages on the physico-chemical properties of the cell by its Editor, E. Gellhorn, 168 pages on the physiological chemistry and 27 pages on the energetics of cell processes by C. Oppenheimer, 172 pages on cellular morphology and the general physiology of development by J. Spek, 83 pages on the process of excitation by L. Ascher, and 44 pages on tropisms by W. von Buddenbrock. As far as the Reviewer is aware there have never previously been brought together in one place such detailed presentations of these various subjects. A volume of this sort is of value not merely from the practical standpoint of making accessible a very large amount of interesting material not hitherto treated in a single textbook, but also in giving the reader a broader and more correct view of the present scope of General Physiology than he is likely to obtain from most other similar sources. Particularly welcome is the inclusion of more physiological chemistry than is generally found in works in this field. The chief defect of the book in its present first edition is the absence of an authors' index and in some of its sections of sufficiently detailed references to the original literature.

M. J.

MEDICAL JURISPRUDENCE. By CARL SCHEFFEL, PH.B., M.D., LL.B. Pp. 313. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, \$2.50.

THE author of this book reverses the usual method; or, rather, looks at the whole subject from a point of view opposite to that which is common. Namely, instead of seeking to show the student how medical matters may effect or influence the solution of various

legal problems, he seeks to enable the student and physician to familiarize himself as to how legal factors effect him in the everyday practice of medicine and surgery and his standing as a sociologic factor in the community. Of course it is just as bad for a physician to endeavor to be his own lawyer as it is for anyone else and the author does not desire his book to be used for any such purpose. Altogether his work is well done. It is written in plain and simple English. There is no padding and it will be well for every young physician to study it; he would save himself from getting into trouble by so doing.

C. B.

DYNAMIC RETINOSCOPY. By MARGARET DOBSON, M.D., LOND.
Pp. 56; 11 illustrations. New York: Oxford University Press,
1931. Price, \$2.50.

THE apparent purpose of this monograph is to champion the advantages of refracting without a cycloplegic, and, therefore, will have an immediate appeal to those who are so minded, or schooled, to begin with. By the same token it may not appeal to others who consider a cycloplegic necessary. Although titled Dynamic Retinoscopy only eleven pages of a total of fifty-five deal with this subject; the other chapters being a consideration of retinoscopy in general, muscle balance and accommodation and convergence.

The price is excessive.

F. A.

DISEASES OF THE GUMS AND ORAL MUCOUS MEMBRANE. By SIR KENNETH GOADBY, K.B.E., M.R.C.S., L.R.C.P., D.P.H. (CANTAB.), Lecturer on Bacteriology of the Mouth, Dental Department, University College Hospital. Pp. 496; 146 illustrations. Fourth Edition. New York: Oxford University Press, 1931. Price, \$13.00.

THE contents of this book are far more comprehensive than indicated by the title. In addition to disease of the gums and oral mucous membrane proper, the author deals extensively with dental caries and its sequelæ—dento-alveolar abscess, acute and chronic, diseases of the alveolo-dental articulation (pyorrhea alveolaris), tumors of the jaws, neuralgia and mouth neuroses. His principal object is to keep before the reader the relationship of infection and disease in the mouth to diseases of the body as a whole. Special attention is called to the chapters on diseases originating from mouth infection and on diseases with oral symptoms. The author's views are to be regarded as sane and reliable when evaluating the importance of oral infection as related to disease elsewhere in the body, and the internist will find in the book a valuable guide in this respect. Aside from a few reproductions of Roentgen ray films, the illustrations are excellent.

R. I.

BOOKS RECEIVED.

NEW BOOKS.

- A Textbook of Laboratory Diagnosis.* By EDWIN E. OSGOOD, M.A., M.D., Assistant Professor of Medicine and Biochemistry, Director of Laboratories, University of Oregon, School of Medicine, and HOWARD D. HASKINS, M.D., Professor of Biochemistry, University of Oregon, School of Medicine. Pp. 475; 21 figures and 6 colored plates. Philadelphia: P. Blakiston's Son & Co., 1931. Price, \$5.00.
- The Thomsen Hemagglutination Phenomenon.* By V. FRIEDENREICH. Pp. 138; illustrated. Copenhagen: Levin and Munksgaard, 1930.
- Approved Laboratory Technic.* Prepared under the Auspices of The American Society of Clinical Pathologists. By JOHN A. KOLMER, M.D., DR.P.H., D.Sc., LL.D., Professor of Pathology and Bacteriology, Graduate School of Medicine, University of Pennsylvania, and FRED BOERNER, V.M.D., Associate Professor of Bacteriology, Graduate School of Medicine, University of Pennsylvania; Assisted by C. ZENT GARBER, A.B., M.D., Associate in Pathology, Peking Union Medical College, and Committees of The American Society of Clinical Pathologists. Pp. 663; 300 illustrations, 11 plates. New York: D. Appleton & Co., 1931. Price, \$7.50.
- Phantastica, Narcotic and Stimulating Drugs.* By LOUIS LEWIN. Pp. 335. New York: E. P. Dutton & Co., 1931. Price, \$3.75.
- The Conquest of Old Age.* By PETER SCHMIDT, M.D., Translated by EDEN and CEDAR PAUL. Pp. 307; 40 plates. New York: E. P. Dutton & Co., 1931. Price, \$5.00.
- A Life of Joseph Priestley.* By ANNE HOLT. With an Introduction by FRANCIS W. HIRST. Pp. 221; 1 illustration. New York: Oxford University Press, 1931. Price, \$3.50.
- Transactions of the Association of American Physicians, vol. 46, 1931.* Pp. 379; illustrated.
- The Ingenious Dr. Franklin.* Selected Scientific Letters of Benjamin Franklin. Edited by NATHAN G. GOODMAN. Pp. 244; illustrated. Philadelphia: University of Pennsylvania Press, 1931. Price, \$3.00. For review see p. 122.
- Medical Psychology.* Monograph Series No. 54. By WILLIAM A. WHITE. Pp. 141; 4 illustrations. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1931.
- The Commoner Nervous Diseases.* By FREDERICK J. NATTRASS, M.D. Dunelm., F.R.C.P. London, Assistant Physician, Royal Victoria Infirmary, Newcastle-upon-Tyne. Pp. 218; 15 illustrations. New York: Oxford University Press, 1931. Price, \$4.00.
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- Infections of the Kidney.* By MEREDITH F. CAMPBELL, M.D., F.A.C.S., Attending Urologist, Babies Hospital, New York Nursery and Child's Hospital; Assistant Visiting Urologic Surgeon, Bellevue Hospital, New York. Pp. 343; 40 illustrations. New York: Harper & Brothers, 1931. Price, \$3.00.

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- The Black Death and Men of Learning.* By ANNA MONTGOMERY CAMPBELL, Assistant Professor of History, New Jersey College for Women. Pp. 210. New York: Columbia University Press, 1931. Price, \$3.00.
- The Medical Clinics of North America, Vol. 15, No. 3 (Chicago Number, November, 1931).* Pp. 227; 53 illustrations. Philadelphia: W. B. Saunders Company, 1931.
- How's Your Blood Pressure?* By CLARENCE L. ANDREWS, M.D., Attending Physician and Medical Chief at the Atlantic City Hospital. Pp. 225. New York: The Macmillan Company, 1931. Price, \$2.50.
- The Ethno-Botany of the Maya.* Publication No. 2 of The Tulane University of Louisiana, Middle American Research Series. By Ralph L. Roys. Pp. 359. New Orleans: The Department of Middle American Research, The Tulane University of Louisiana, 1931.
- Typhoid Fever.* By WILLIAM BUDD, M.D., F.R.S. Pp. 184; 5 illustrations, 1 in color. New York: American Public Health Association, 1931. Price, \$5.00.
- Experimental Studies on the Course of Paratyphoid Infections in Avitaminotic Rats.* By H. C. A. LASSEN. (Translated from the Danish by HANS ANDERSEN, M.D.) Pp. 248; illustrated. Copenhagen: Levin and Munksgaard, 1931.
- Blood Sugar in Normal and Sick Children.* By ELISABETH SVENSGAARD. Pp. 245; illustrated. Copenhagen: Levin and Munksgaard, 1931.
- The Truth About Birth Control. Pamphlet No. 4.* By NORMAN E. HIMES. Pp. 28. New York: The John Day Company, 1931. Price, 25 cents.

NEW EDITIONS.

Elementary Anatomy and Physiology. By MARY REES MULLINER, M.D., Director of the American School for Physical Education. The Physical Education Series. Edited by R. TAIT MCKENZIE, M.D., M.P.E., LL.D., Professor of Physical Education and Physical Therapy, University of Pennsylvania. Pp. 448; 313 engravings in black and color. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1931. Price, \$4.75.

A useful book for students of physical education and nurses who do not desire a large general textbook which necessarily includes considerably more material than they have time to digest. In this edition the physiology of the various systems has been more fully treated and numerous other details brought up to date by consulting the last editions of Gray's Anatomy and Starling's Physiology.

The Physiology of Muscular Exercise. By the Late F. A. BAINBRIDGE, M.A., M.D. Cantab., D.Sc., F.R.C.P., F.R.S., Professor of Physiology, University of London. Rewritten by A. V. BOCK, M.D. Harvard, Ph.D. Cambridge, Assistant Professor of Medicine, Harvard; Physician, Massachusetts General Hospital, Boston, and D. B. DILL, Ph.D. Stanford, Assistant Professor of Biochemistry, Harvard. Pp. 272; 46 illustrations. Third Edition. New York: Longmans, Green & Co., 1931. Price, \$5.00.

Medical Electricity for Students. By A. R. I. BROWNE, Member of the Society of Radiographers; Radiographer at the Royal Alexandria Infirmary. Pp. 245; 88 illustrations. Third Edition. New York: Oxford University Press, 1931. Price, \$4.00.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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A Note on the History of Pellagra in the United States.—It is of interest to note that it was not until 1907 that pellagra was recognized in the South. In spite of the fact that the disease was not known, WHEELER (*U. S. Pub. Health Rep.*, 1931, 46, 2223) contends that pellagra was present in the United States and that the only argument against the incidence of pellagra in the South to any considerable extent prior to its recognition in 1907–1908 was the fact that it was not so recognized. He calls attention to the fact that in the first seven editions of Osler's *Practice of Medicine* the statement was made that it has not been observed in the United States. Other standard textbooks of the time make no reference to pellagra. However, when this very common disease in the South was recognized a group of older practitioners of medicine were circularized for the purpose of asking them whether or not they had seen cases before this particular period, and it was found that a goodly number of them had observed the disease but did not know what it was. This fact alone would destroy one of the arguments of those who contend that the disease is of bacterial origin. One of the reasons advanced that the disease is primarily bacterial is that there was an epidemic of pellagra in 1907–1908; such an epidemic the epidemiologists believed could occur only when the disease is a disease transmitted from man to man. Observations that have been made on the incidence of pellagra in recent years have shown that the disease is very much more prone to occur in large numbers following periods of economic stress. Such a period existed in 1907–1908. Likewise, there have been known increases of the disease in 1915, 1921 and 1930. At the present time in Louisiana, which probably holds good in other southern States, more pellagra has been reported than any time in recent years. As a matter of fact, in the 6 weeks' period, beginning

June 30, more cases were reported than of any other of the reportable diseases, exceeding by far the next disease in frequency. These data may be taken to substantiate the idea that dietary inadequacy plays some rôle in the production of the disease. It is reasonably obvious why the diet should be inadequate following periods of financial depression. Incidentally, it may be mentioned that only from 10 to 15 per cent of the pellagra cases in a given community will consult a physician. These data have been obtained through field surveys in localities where pellagra is prevalent and where the entire population has been studied. Another observation made by this writer seems worthy of recording, and that is that it is only the out-spoken cases of pellagra who have the diagnostic triad of dermatitis, diarrhea and dementia and it is only such cases that are actually reported to the health authorities.

SURGERY

UNDER THE CHARGE OF
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Acute Craniocerebral Injuries.—OCHSNER (*Am. J. Surg.*, 1931, 12, 523) believes that edema of the brain is the most important pathologic lesion as it is the most frequently encountered. The extent of the edema varies considerably. Not infrequently a vicious circle is produced, *i. e.*, as a result of the edema there is interference with the venous return, which causes a diminished absorption of the cerebrospinal fluid, which in turn produces an increased intracranial pressure. Contusion and laceration are found in the more extensive injuries of the cerebrum and vary largely in degree. Lacerations are usually associated with lesions of the cranium, whereas contusions frequently are not. Hemorrhage is of two types, intradural and extradural. Associated with every cerebral injury from the slightest contusion to the extensive laceration, there are varying degrees of hemorrhage. Intradural hemorrhage is a result of injury to the brain substance, whereas extradural hemorrhage occurs as a result of injury to the middle meningeal artery or rarely to the lateral venous sinus. Subdural hemorrhage is of importance because of sequelæ which may develop such as sterile meningitis, abnormal accumulation of cerebrospinal fluid, which may subsequently lead to cerebral atrophy and localized cystic changes occurring in hematomas. Fractures of the skull are divided into two main types, those of the vault and those of the base. Simple and comminuted fractures of the vault are of no significance clinically. Fractures of the base are of great significance because almost invariably they are compound fractures in that fracture extends into the nose, nasal accessory sinuses, mastoid process, or middle ear. The finding of blood in the cerebrospinal fluid is of utmost importance because of the subsequent sequelæ which may develop, because of the blood in the subarachnoid space. The treatment is one of conservatism basically.

Mesenteric Vascular Occlusion.—LARSON (*Surg., Gynec. and Obst.*, 1931, 53, 54) says that the most common causes of arterial embolism were mural cardiac thrombi. The most common causes of arterial thrombosis were arteritis and arteriosclerosis of the mesenteric artery. Venous mesenteric occlusion most often resulted from a septic process either in the gastrointestinal tract or the pelvis and was of the ascending type. It followed hepatic disease in 25 per cent of cases. The vascular occlusion affected the arteries in 14 cases, the veins in 16 and both veins and arteries in 6. In all cases of arterial occlusion and in all but one of the cases of venous occlusion, the superior mesenteric vessels were involved. A definite source of the vascular occlusion either was unknown or was problematic in 8 of the 36 cases. Hemorrhagic infarction resulted in 31 of the 36 cases. When intestinal infarction took place, it was generally manifested by symptoms of intestinal obstruction which were indistinguishable from those of other types of obstruction. Typically it occurred in an elderly person, starting with extremely severe colicky abdominal pain, nausea, vomiting and diarrhea. The vomitus and the diarrheal stool were often mixed with blood; occasionally complete retention of feces was noted. Soon the pain became steady, the shock more severe, the abdomen distended and tympanitic and the temperature and pulse, which at first were likely to be subnormal, became progressively elevated. Later signs of general peritonitis developed and death took place. The symptoms produced by closure of the main trunk were indistinguishable from those produced by obstruction of the branches. The course of the disease is short and may be less than 48 hours. In at least 53 per cent of the cases definite peritonitis was present and in 55 per cent bloody ascites was noted.

Autointoxication and Shock.—MASON and LEMON (*Surg., Gynec. and Obst.*, 1931, 53, 60) state that fresh tissue extract administered intravenously lowers blood pressure sufficiently probably to endanger patients who are in a critical condition. Fresh tissue extract is a very potent factor in producing intravascular coagulation and sublethal doses of autolyzed liver-tissue extract causes marked circulatory disturbances; the lethal dose being 7 to 8 cc. for the dog. Treatment of autolyzed liver-tissue extract with tannic acid does not precipitate the toxic fraction. The marked rise in blood pressure following sublethal doses of autolyzed tissue suggests the possibility that foci of infection may liberate a toxic substance which elevates blood pressure.

Acute Gonococcal Epididymitis.—GARVIN (*Am. J. Surg.*, 1931, 12, 502) says that gonococcal epididymitis is the most frequent disease of the testicle and the most prominent cause of male sterility. Chemical irritation, instrumental trauma and sexual excitement with an over-distended bladder in the presence of either an active or latent gonococcal infection, are the most common causes of epididymitis. Epididymitis is the result of a mechanical transference of gonococci-laden pus from the posterior urethra and seminal vesicles down to the vas to the epididymis. It is peritubular extension and not intratubular, involving principally the globus minor and other portions of the epididymis by periepididymal extension. It is a true epididymitis and not an epididymo-orchitis. Clinical experience leads to the belief that

in the vast majority of cases conservative treatment, rest, scrotal splintage, intramuscular injections of nonspecific protein will yield good results, many cases remaining ambulant. Operative treatment is indicated in the fulminating cases not yielding to conservative treatment and in recurrent cases and in cases not resolving. Thorough eradication of all foci of infection in the posterior urethra, prostate and vesicles is necessary regardless of type of treatment employed.

THERAPEUTICS

UNDER THE CHARGE OF
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Treatment of Muscular Rheumatism by Infiltration of Glucose Solution.—Long having recognized the unsatisfactory results obtained from the use of a wide variety of medicinal agents, heat, massage and the like, NATANSEN (*Deutsch. med. Wchnschr.*, 1931, 57, 885) experimented with the infiltration of the painful areas by means of local anesthetics in various solutions. He found that a 10 per cent solution of glucose or a mixture of glucose and fructose was almost specific in the relief of pain, being both immediate and lasting in its effects. The author here presents a brief report on the basis of 5 years experience with the 10 per cent sugar solutions. He states that its response to the wide infiltration of the subcutaneous and muscular tissues lying within the painful zone with amounts ranging from 30 to 100 c.cm. is so certainly effective that the failure of the pain to disappear is almost diagnostic in the sense that it indicates some other condition than muscular rheumatism or myalgia as the cause of the pain. Relapses are exceedingly rare and are almost always of extremely brief duration. The method of action is not clear and is not entered into in this place by the author. He suggests, however, that the effects may be due to combined osmotic chemical and mechanical actions. No deleterious effects have been observed. The method is naturally contraindicated in diabetic patients.

The Action of Strophanthin on the Circulating Blood Volume.—Investigations carried out upon patients suffering from decompensated valvular heart disease under conditions of control and with the employment of the trypan-red method of determining blood volume led MIES (*Ztschr. f. Krebsforsch.*, 1931, 33, 460) to the conclusion that strophanthin diminishes the blood volume to a significant degree for from 24 to 36 hours after its intravenous administration. The degree of reduction of blood volume is more or less proportional to the size

of the dose administered. Similar results were obtained from another digitalis body, adovern, indicating the possibility that this is a characteristic of the action of this whole group of drugs. The author suggests that the diminution in blood volume may possibly be a factor in aiding restoration of cardiac efficiency by reducing venous congestion, but he does not feel prepared yet to express an opinion upon the worth of this suggestion.

PEDIATRICS

UNDER THE CHARGE OF

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Thyroidectomy for Thyrotoxicosis in the Young.—GREENE and MORA (*Surg., Gynec. and Obst.*, 1931, 53, 375) report 26 cases in which thyroidectomy was done for thyrotoxicosis in children between the ages of 8 and 16 years. These cases were a part of a series of 1200 consecutive toxic goiter patients who were subjected to operation. There were 22 girls and 4 boys. The chief symptoms and signs were tachycardia, nervousness, goiter, exophthalmos, tremor, loss of weight, palpitation, enlargement of the left side of the heart, irritability, weakness and restlessness. The symptoms corresponded closely to those manifested in adults. The average pre-operative systolic and diastolic blood pressure readings were 132 and 65 mm., respectively. The average postoperative readings were 108 and 72 mm. The average pulse pressure dropped from 67 to 36 mm. after operation. The average pre-operative basal metabolic rate was +34.6. The average postoperative reading was -6.2. All of the glands examined microscopically showed varying degrees of hyperplasia and hypertrophy. One-stage thyroidectomy was done in every instance, with no fatalities.

The Retention Rate of Calcium: Phosphorus in Infants and Children.—STEARNS (*Am. J. Dis. Child.*, 1931, 42, 749) from a consideration of the rate of growth of the various tissues of the body from birth to 1 year of age, and the distribution of phosphorus between the bony and the soft tissues, it is considered that a retention ratio of calcium: phosphorus of between 1.5 to 1 and 2 to 1 is normal for an infant. A retention ratio lower than 1.5 to 1 indicates a more rapid growth of soft tissue than of bone. A ratio of 2 to 1 or more is considered as probably indicative that a calcium shortage in the body is being corrected. From the reported retention of calcium and phosphorus in artificially fed infants, a retention of at least 40 mg. of calcium and from 20 to 25 mg. of phosphorus per kilogram of body weight per day is considered desirable for artificially fed infants. The ratio of retained calcium to phosphorus will be somewhat lower in older children than in infants because of the great increase in the relative amount of muscular tissue during childhood. In a normal child, it is considered that the retention rate will

probably be lower than that observed in infants, but it should be greater than 1 to 1. In older children the absolute retention of calcium and phosphorus per kilogram of body weight may be expected to decrease with the age of the child. A retention of at least 10 mg. of phosphorus per kilogram of body weight per day is desirable even in older children. The retention of calcium should be at least equal to the retention of phosphorus. Retentions of calcium and phosphorus of less than 10 mg. per kilogram of body weight are probably not optimal in very young children.

Treatment of Toxicosis With the Aid of a Continuous Intravenous Drip of Dextrose Solution.—KARELITZ (*Am. J. Dis. Child.*, 1931, 42, 781) treated 21 patients with severe toxicosis by this method and only 3 died, which was a mortality of only 14 per cent. Four patients, who were severely toxic and presented evidence of severe pneumonia before treatment was started, also died. Five other patients who were very toxic but in whom it was not possible to make a diagnosis of toxicosis recovered under this treatment. In the entire group of 30 cases there were 7 deaths or a mortality of 23 per cent. The author believes that the administration of fluid by the continuous intravenous method is a definite improvement in the treatment. The withholding of milk for a longer time, which he believes is as important as any other phase of the treatment, is thus made possible. The entire requirement of fluid is given through the one cannula with the least disturbance of the child. Acidosis and concentration of the blood respond rapidly to this form of treatment. It supplies water, salt and dextrose in a hypertonic solution at a rate fast enough to produce diuresis at first, and later slow enough to permit proper assimilation. Blood, epinephrin, caffeine and digitalis can be given through the same cannula. During the time of the intravenous flow, the gastrointestinal tract, as well as the entire body, is given a much needed rest. Quiet sleep usually ensues, vomiting usually stops, thirst is created, and in many cases the diarrhea is favorably influenced. The child is spared the pain of the subcutaneous injection of the fluid and the occasional complication resulting from intraperitoneal injection, and the doubt of its absorption is obviated. The author confirms the opinion of Schick that the requirement of fluid is much less than is customarily thought to be. Certain facts must be constantly kept in mind. Treatment must be radical and prompt as soon as diagnosis is made. Supportive treatment, such as the administration of epinephrin and caffeine, should be given as indications arise. All cases of toxicosis should be considered as severe. The intravenous administration of dextrose and transfusion should be employed promptly, and the minimum period during which milk should be withheld should be from 24 to 48 hours, or until detoxification is complete. Once the feeding of milk is commenced it should be given in small amounts of from 5 to 10 cc., and increased slowly. When there is a relapse, treatment should be started again from the beginning with the intravenous method of administering dextrose, transfusion of blood and abstinence from milk. Patients with intercurrent infections especially otitis and abdominal distention should be treated actively.

Skin Temperatures of Children.—TALBOT (*Am. J. Dis. Child.*, 1931, 42, Part II) made studies of skin temperatures in children by means of a thermocouple. There is a local variation of the temperature of the skin over different parts of the body, even in normal children; the temperature of the trunk being highest, the face next and the extremities lowest. The temperature of the feet tends to be lower than that of the hands. Surrounding temperature has a definite effect on the temperature of the skin of the body even when it is clothed. The cooler the room the lower the temperature of the skin. There is also a seasonal effect on the temperature of the skin. This study showed that humidity within the limits of room temperature and room humidity had no effect on skin temperature. There is a rapid loss of heat from the surface of the body on exposure. This affects the face least, the body next and the extremities most. There is a greater variation in the reaction of the extremities to different surrounding temperatures than in other parts of the body. This suggests that the extremities act as safety valves for the conservation or elimination of heat. During fasting the temperature of the skin, as well as that of the body becomes reduced. Exercise has a very definite effect on the skin temperature. During the first few minutes of exercise the temperature of the skin falls and later rises. This may be of profound physiologic importance, and suggests that when exercise is first commenced heat is retained in the body in order to increase the efficiency of the muscles. This study gives further evidence that the heat-regulating apparatus of the premature infant is not developed. The temperature of the skin, as well as that of the body, is affected directly by the surrounding temperature and to a greater degree than in normal babies. Studies were made of the effect of fever on subjects with different body temperatures. These were grouped in such a way that the skin temperature for different fevers and different room temperatures are now available and are presented as possible standards of expected skin temperatures for different body and room temperatures. The skin temperature was recorded for a number of cretins with lowered metabolic rates. Some of them were studied after the metabolism had been elevated by the use of thyroid gland. When heat production was found increased, the temperature of the skin was increased.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Ovarian Hormone Therapy.—The results obtained in treating 63 cases of ovarian deficiency, as evidenced by amenorrhea of various types with a water soluble ovarian preparation known as "oestrin"

have been described by SMITH (*Lancet*, 1931, 220, 464). He gives a course of daily hypodermic injections of 10 units for from 6 to 18 days, often repeating the course if no results were obtained from the first series. In cases of primary amenorrhea the results were negative. These were individuals who had passed the normal age of puberty without any signs of the onset of menstruation. In primary menstrual irregularity, menstruation became regular in 6 out of 19 cases. These were individuals in whom menstruation had never occurred from the onset at less than 3 or 4-month intervals. The best results of the entire series were obtained in cases of secondary amenorrhea which developed after some years of regular menstruation. In these cases positive results were obtained in 20 out of 37 cases (54 per cent). In 12 of the successfully treated cases the subsequent rhythm of menstruation was normal without any further treatment and in 2 of these patients, who had been sterile, pregnancy subsequently occurred.

Leukoplakic Vulvitis.—This curious, annoying and sometimes dangerous condition has been discussed by COUNSELLER (*Minn. Medicine*, 1931, 14, 312), of the Mayo Clinic, who states that in the early stages the treatment usually consists of the use of emollients and salves, which have however, only a temporary effect. Roentgen rays and radium often stimulate the disease and may produce a burn. If a malignant lesion is not present, he believes the ideal treatment consists of sectioning the internal pudic nerve, thereby anesthetizing the vulva and permanently relieving the pain and pruritus, which are so constant and so annoying in this condition. This has been done at the Mayo Clinic with very satisfactory results although they make no claim for the originality of the procedure. Following the operation the patient should be submitted to careful examination at least twice a year and if there is any question as to the presence of a malignant lesion, simple vulvectomy should be performed in cases in which the malignancy is graded 1 or 2. If the tumor is of a higher grade of malignancy or if there is lymphatic involvement in a case of lower grade malignancy, radical vulvectomy with bilateral dissection of the gland-bearing area should be performed. If the condition of the patient in whom a malignant neoplasm is found does not justify radical removal, then he advises section of the internal pudic nerve and the use of radium as palliative measures.

Carcinoma of Female Urethra.—In spite of the fact that the reports in the literature indicate that the results of treatment of carcinoma of the urethra by operation show less than 20 per cent living patients at the end of a year, MIKULICZ-RADECKI (*Zentralbl. f. Gynäk.*, 1931, 55, 2922) sounds a bit optimistic over the results which have been obtained in Stoeckel's Clinic in Berlin. They have treated these cases by means of a combined technique, taking into account not only the primary tumor but also the regional lymphatic glands. The primary tumor is treated with radium irradiation, the maximum dose being 2000 mg.-hrs., although in the less advanced cases 1000 mg.-hrs. may be sufficient. The glands in the inguinal region and along the large pelvic vessels are removed surgically whenever possible. Of 4 cases which he has treated by this method all are living over a year after the treatment, 3 of them living from 1½ to 3 years completely free from recurrence and with complete urinary continence.

OPHTHALMOLOGY

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Retinal Changes in Hypertension and in Renal Disease.—According to ROLFE (*Arch. Ophthalm.*, 1931, 6, 433), the lesions seen in the eye grounds of patients with hypertension and renal disease consist of various combinations of vessel changes with hemorrhages, "hard white" and "cotton wool" patches, and edema of the retina and of the optic disc. The vessel changes may be either spastic constriction or sclerosis of the arteries or dilatation of the veins. Histologically, in the eyes of people who have died of nephritis, edema is found in the optic nerve and edema and hemorrhages in the various layers of the retina between the retina and the choroid. Sclerosis of the retinal arteries may or may not be present. When present it is similar to sclerosis elsewhere. The white patches seen ophthalmoscopically are represented by various types of degeneration of the retinal tissue—varicosities of a group of nerve fibers, lipid deposits in the retinal tissue, areas of destruction of retinal tissue with fat or fibrous deposits and with large phagocytic cells filled with fat. The histologic changes are essentially the same in retinitis of hypertension. Renal lesions may be classified into three main groups: nephrosis, glomerulonephritis and renal sclerosis, which last may be benign or malignant. In nephrosis retinal lesions do not occur, since all the changes found in the retina and its vessels in diseases of the kidney are due primarily to hypertension. Destruction of kidney tissue in itself does not cause retinal changes. Hypertension probably causes sclerosis of the retinal arteries, and, through ischemia, the result of spasm or sclerosis or both, the retinal degeneration. Nitrogenous or other toxic retention is certainly not more than a contributory factor in the production of retinitis. Cholesterolemia is not a necessary factor. The origin of the edema of the nerve heads has not yet been determined. It may be toxic or ischemic or due to increased intracranial pressure from edema of the brain. Narrowing of the retinal arteries without other changes is seen chiefly in pregnant women and in acute glomerulonephritis. It is seen more frequently in association with other more severe changes. Sclerosis of the retinal arteries is found almost constantly in persons who have suffered from hypertension for a few years. It may occur in patients with general arteriosclerosis but without hypertension. Retinal arteriosclerosis in association with hemorrhages and sharply defined white patches, so-called arteriosclerotic retinopathy, is frequently seen in patients with hypertension but with normal renal function. Papilledema with "cotton wool" and hard patches and hemorrhages with or

without sclerosis of the arteries make up the typical nephritic neuroretinitis which is seen chiefly in malignant sclerosis and in the final decompensated stages of chronic glomerulonephritis but at times when renal function is normal. Narrowing of the retinal arteries means spasm and indicates only that the blood pressure is elevated. Sclerosis of the retinal arteries usually means that hypertension has existed for some time and that arteries elsewhere are similarly affected. It is not evidence of renal disease. It may indicate a tendency to apoplexy. Hemorrhages and sharply defined white patches in the retina do not indicate any special liability to death from renal disease, but they do suggest the possibility of cardiac or cerebral complications. They do not place a definite limit on life. The retinitis characterized by "cotton wool" patches and papilledema has been variously designated as nephritic retinitis, malignant hypertension neuroretinitis and retinitis of malignant hypertension. It indicates, in general, death within 2 years—usually from uremia but at times from apoplexy, cardiac failure or intercurrent disease. Occasionally, however, such a retinitis may clear up and renal failure may not develop. Papilledema occurring alone may be the first indication of nephritic retinitis or it may indicate increased intracranial pressure from edema or tumor of the brain, and observation is necessary for its final interpretation.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The After-effect of Epinephrin Chlorid and Ephedrin Hydrochloride on the Mucosa of the Nasal Septum.—The site of action, as well as the *modus operandi* of epinephrin and ephedrin when used topically, is a greatly debated question. Purposing to determine, if possible, the mode and site of action of these two drugs when applied locally to the nasal mucosa. Fox (*Arch. Otolaryngol.*, 1931, 13, 255) reports results of histologic studies on septal tissues removed from 106 healthy adult rabbits. Under varying experimented conditions the nasal septums were removed and the mucosa prepared for microscopic examination according to techniques described in the text. It was concluded that a 1 to 1000 solution of epinephrin chlorid caused the mucosal vessels, at first constricted, to dilate after four hours and allow blood to escape into the perivascular bed and a chemotaxis-like behavior of the leukocytes; whereas, in the case of ephedrin hydrochlorid (2 per cent) the vessels remained unchanged after the 4-hour period. The author summarized by saying: "It seems rather, that epinephrin exerts some direct injury to the vessel walls."

The Pharmacodynamics of Local Mucous Membrane Medication.—The therapeutic objective of most localized medication is the production of astringency, antipathogenesis ranging from unfitting the

mucosa for bacterial growth and absorption of pathogenic products to complete destruction of microorganisms or mechanical protection, or a combination of these effects. Any therapeutic endeavor not considerate of the physiology and pathology of the tissues and the pharmacodynamic action of the drug employed, as based on those factors is empirical at best. Enumerating as important pharmacodynamic points such matters as insulation, viscosity, solubility, hydrogen-ion concentrate and the multiple effect of most drugs, SCHEFFEL (*Laryngoscope*, 1931, 41, 274) discusses these factors as they relate to rational local mucosal medication. Attention is directed to the fact that: (1) Aqueous solutions or vehicles are practically free from the insulating drawbacks that appertain to some oily solutions; (2) that vehicular viscosity should depend largely upon the rate of absorbability desired; (3) that maximal therapeutic effects are dependent not only on the relative solubility of drug in its menstruum but also on a solubility; (4) that a hydrogen-ion concentration should closely approximate that of the tissues to be treated. The writer admonishes careful consideration of these basic principles before accepting or rejecting many preparations as having a scientific basis for rational topical therapy of mucous membranes.

RADIOLOGY

UNDER THE CHARGE OF

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Irradiation Therapy in Functional Ovarian Disorders.—FORD (*Radiology*, 1931, 16, 936) relates the results in 47 cases in which radiotherapy was administered primarily for habitual amenorrhea or for oligomenorrhea or sterility associated with these conditions, and in 29 cases in which this treatment was given primarily for dysmenorrhea. In the first group, by exposure of the ovaries or hypophysis to approximately 5 to 10 per cent of an erythema dose of Roentgen rays, reestablishment of menses was obtained in 26 of the 47 cases. Menstruation has continued regularly in the majority of these patients for periods varying from a few months to two years. Seven pregnancies have occurred among 6 of the 24 married patients in this group, all of whom had previously been sterile. Two pregnancies were continuing at the time of this study, 2 have terminated in miscarriage, and 3 full-term children have been born, two of whom are living and well. Among the 29 patients with dysmenorrhea, relief of pain followed irradiation in 18. Although the duration of relief is extremely variable, by repeated irradiation a satisfactory result has been maintained as long as 3½ years in 1 case. No evidence was found that repetition of treatment at intervals of 3 months or longer has adversely affected ovarian function.

Radiography with Enlargement (Microradiography).—It is known that if an object is moved away from the film and toward the source of radiation an enlarged roentgenographic image is obtained, but it is blurred, because the focal spot is not strictly a point but an area of appreciable size and a penumbra necessarily results. This disadvantage has been overcome by VALLEBONA (*Radiol.*, 1931, 17, 340). He places a very small window between the object to be radiographed and the target of the tube; as a result the rays from the target follow a rectilinear path and produce an unblurred, enlarged image. The accessory apparatus is simple and consists of a series of lead disks with holes in them varying in size from 1 or 2 mm. to one half of a decimillimeter. The greater the distance of the object from the film, the smaller is the aperture required. According to the distance, the appropriate disk is selected and attached to the window of the tube cover. A magnified, sharp image is obtained. The method is especially applicable to the study of bone structure, and the author has used it successfully in cranial roentgenography.

The Roentgenologic Significance of Pyloric and Prepyloric Deformities.—According to CAMP (*Radiology*, 1931, 16, 847) it is a peculiar but significant fact that the pyloric segment of the stomach which is most accessible to roentgenologic examination, offers more diagnostic difficulties than any other. Sixty per cent of all gastric cancers, 69 per cent of benign gastric tumors and approximately 10 per cent of gastric ulcers are found in this area. This region is also a favorite site for spasm which is the arch deceiver of the roentgenologist. Fluoroscopic examination is indispensable for study of the pyloric segment, and is best accomplished by having the patient at first take only one or two swallows of the barium mixture which should be manipulated by the examiner so as to depict the internal topography of the stomach. Later the stomach can be completely filled with barium to study the gastric tonus, peristalsis and motility. In the consideration of ulcerating lesions in the pyloric region, it is noteworthy that here carcinoma outnumbered benign ulcer. Prepyloric ulcers also have a greater tendency to become malignant than ulcers elsewhere. Thus when ulceration is demonstrable the odds are in favor of a malignant lesion. Because of accessibility to examination pyloric cancer should be diagnosed earlier than cancer in other parts of the stomach. This is perhaps the case, yet the disease is not being diagnosed early enough. Of 2078 cases of gastric cancer seen at The Mayo Clinic between the years 1920 and 1924, 50 per cent were excluded from exploration as hopelessly inoperable, 25 per cent were explored but found to be inoperable, and resection was possible only in the remaining 25 per cent. Pyloric cancer may take the form of (1) a frank polypoid tumor with or without ulceration; (2) a scirrhus infiltrative growth; (3) a malignant ulcer, or (4) a benign tumor which has undergone malignant changes. The first form can scarcely escape discovery. Scirrhus cancer may be imitated by syphilis, prepyloric ulcer, pylorospasm and hypertrophic pyloric stenosis. The differential diagnosis of cancer rests on the persistence of the deformity, the slightly serrated outline, loss of flexibility, absence of peristalsis, obliteration of mucosal markings and the presence of a mass coinciding with the defect. An ulcer with a niche less than 2.5 cm.

in diameter has only 1 chance in 10 of being malignant; if it is larger than this the chances are 3 to 2 that it is malignant, and if larger than 3.5 cm. it is certainly cancerous. A high percentage of benign tumors undergo malignant change, and they are always open to suspicion.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Encephalitic, Idiopathic and Arteriosclerotic Parkinsonism.—KESCHNER and SLOANE (*Arch. Neurol. and Psychiat.*, 1931, 25, 1011) report a clinicopathologic study of 7 cases of Parkinsonism. These cases are presented in detail both clinically and pathologically. They remark that "whereas the clinical course of the syndrome depends to a great extent on the nature of the pathologic process, it is obvious that its symptomatology does not depend entirely on the structural changes found in the nervous system after death." The substantia nigra was involved in every case except one diagnosed clinically as arteriosclerosis in which it showed only evidences of vascular sclerosis. The lesions in the locus cæruleus paralleled, to some extent, those in the substantia nigra. The pallidum seemed to have been mostly affected in the idiopathic cases. As to the involvement of the other basal ganglia, it did not seem to make much difference whether the case was encephalitic, idiopathic, or arteriosclerotic, so far as the site of the pathologic process was concerned. The changes in the cells were typical of a chronic degenerative process. The cases seemed to show that the generally accepted view that the neostriatum and pallidum are the predominating sites for the lesions in idiopathic Parkinsonism and the substantia nigra in encephalitic Parkinsonism must not be adhered to too slavishly in attempting to differentiate pathologically between these two types of disease. The diffuseness of the chronic inflammatory lesions in encephalitic Parkinsonism, the extensive secondary changes in the brain following disease of the vessels in the arteriosclerotic and the widespread degenerative lesions in the idiopathic form make attempts to correlate the clinical picture with the anatomic observations an unusually difficult task. The authors conclude "there is too little definite information as to the effects of disturbances of function and their relation to structural changes in the neural mechanism as the basis of the symptomatology of the various diseases of the extrapyramidal system. This is especially true in Parkinsonism. Hence the futility of attempting a definite differentiation between the various types of Parkinsonism without taking into consideration the history, symptomatology, clinical course and pathologic observations. Practically all one may say is that in many cases the presence or absence

of certain signs or symptoms of Parkinsonism during life will not always justify the clinician in giving an opinion as to what may be found at postmortem examination."

Dreams and Their Relationship to Recent Impressions.—MALAMUD and LINDER (*Arch. Neurol. and Psychiat.*, 1931, 25, 1081) present the results of experimental investigations in 16 cases undertaken with the purpose of finding out whether the factors uniformly occurring in dreams can be demonstrated experimentally. These observations form the central feature of the psychoanalytic theory of dream psychology. The psychoanalytic theory regards the dream as representative of a more or less disguised fulfillment of a wish that is otherwise repressed and does not gain access to the consciousness of the person when awake. This wish, which at one time has been actually experienced, but not gratified, remains as a latent force in the subconscious level and reappears in the dream only when stimulated by a suitable recent occurrence. The procedure was thus: The subject is taken into a quiet room and engaged in conversation for 5 minutes. The subject is allowed to look at a given picture for 30 seconds. He is conversed with for 5 more minutes. Then he is asked to describe the picture until his descriptive powers are exhausted. He is told that if he should have any dreams during the night he should remember them and give them to the examiner the next day. The patients were all mental cases in hospitals having varied diagnoses. The results of these experiments were as follows: (1) The factors regarded by the psychoanalytic theory as uniformly occurring in dreams were demonstrated in the dreams of a number of patients. (2) It is possible to produce them experimentally. (3) Some contents in the recent experiences of our subjects that were left out in their descriptions were subsequently shown to recur in their dreams. (4) These contents seemed to have a definite relationship to experiences in the earlier life of the person. (5) These latter two experiences "were found to be definitely related to those problems in the subjects' lives that, as far as could be judged, formed the central feature of the disease process."

The Incidence and Significance of Fingernail Biting in Children.—WECHSLER (*Psychoanalytic Review*, 1931, 18, 201) presents a study of 3000 children of both sexes, ranging from 1 to 17 years of age. He finds that fingernail biting under the age of 3 does not occur. The tendency first begins to manifest itself during the fourth year, rises slightly in the next, and then suddenly jumps up at the age of 6, from which year it maintains a fairly constant level until puberty. At the age of 12 for girls and the age of 14 for boys the percentage once more rises and continues at a high peak for 2 years. It then quickly recedes to a very low level at which it continues for the entire adult period. It becomes apparent that there is some connection between the incidence of fingernail biting and various periods of psychosexual development. The author discusses this relationship attempting a correlation between the two stating that nail biting is not a habit but a symptom of the oedipus situation and all treatment is "doomed to fail" unless the cause is attacked.

Report of Results from Use of Ketogenic Diet and Ketogenic Diet With Water Restriction in a Series of Epileptics.—DOOLITTLE (*The Psychiatric Quarterly*, 1931, 5, 2, 225) presents the results of his study of 25 epileptics with water restriction and modified ketogenic diet. These patients for a period of 4 weeks were segregated and given a regular diet and allowed to drink all the water they desired, day and night. The quantity of water consumed was recorded. All sedation was taken away from these cases with the exception of 2, with whom this was impossible. After a preliminary fasting of 12 hours, all these patients were placed on from 25 cc. to 44 cc. of 40 per cent cream every 4 hours with no water intake. This lasted for 40 hours. Following this all patients were put on a diet having acid ash, moderately ketogenic about as follows: Fat 140 to 180 gm., proteid 50 gm., carbohydrates 50 gm. At the same time these patients were placed on water restriction varying with the individual from 300 cc. to 630 cc. in 24 hours. The results observed by the writer may be tabulated as follows: (a) In the period of observation prior to water restriction, there were 67 petit mal and 116 grand mal seizures in the group per week. While on water restriction there were 80 petit mal and 75 grand mal seizures per week. Following the treatment the petit mal seizures dropped to 25 and the grand mal seizures rose to 87 per week. (b) Two cases showed very marked mental improvement. (c) The seizures did not decrease in the cases under dehydration with an increase in body temperature. Dehydration with hyperthermia was a serious combination. (d) Under ketogenic diet the cases showing the greatest tendency toward improvement were those of the idiopathic type. (e) Out of the 25 cases in which the modified ketogenic diet and water restriction therapy was tried, the author found one with whom he believed it could be called a success. Six patients showed quite marked improvement with respect to the grand mal seizures. Two showed slight improvement. The rest showed no improvement or apparently had an increase of seizures under treatment.

Encephalitis Periaxialis Diffusa: Schilder-Foix Disease.—COENEN and MIR (*L'Encephale*, 1931, 26, 357) describe a case of Schilder's disease in a man aged 41 years, which began with loss of sight in the left eye, headache, stiffness of the right arm, and a burning sensation round the abdomen; deafness of the left ear came on soon after, and within 3 weeks his right leg and left arm became weak and sensation was completely lost on the left half of the body. Both optic disks were swollen and pale. The patient died 43 days after the onset of the disease. At postmortem diffuse sclerosis and demyelination of the white matter of the cerebral hemispheres was found, with more discrete patches in the pons and cerebellum. The cortex was everywhere spared. In the histologic examination the most noteworthy finding was the large number of "mucocytes" in the areas of more recent demyelination. The authors confirm the findings of Grynfeldt and Pelissier and of Bailey and Schaltenbrand that mycocytes rise from acute swelling of the oligodendroglia by inhibition of the early products of myelin disintegration (protagonoid substances). They consider that in Schilder's encephalitis the disease process attacks first the oligodendroglia and that the degeneration of myelin is secondary to this.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Hypertension in Relation to the Bloodvessels of the Medulla Oblongata.—Several workers had previously attempted to show that hypertension was due to arteriosclerosis of the bloodvessels of the medulla oblongata. In the present study TUTHILL (*Arch. Path.*, 1931, 11, 760) examined the bloodvessels of the medulla oblongata in the region of the obex in 24 cases of hypertension of varying duration, and in 35 cases in which the blood pressure was normal. In the cases with hypertension there were only 12 which showed an arteriosclerosis of the vessels of the medulla oblongata. The arterioles in the region of the olives and larger vessels in the center of the medulla were chiefly affected. Of the only 12 cases of hypertension slight or no arteriosclerosis of the vessels was found. Among the 35 cases in which the blood pressure was normal 6 showed arteriosclerosis of the vessels of the medulla oblongata. In none of the cases examined was arteriosclerosis confined solely to the vessels of the medulla oblongata. The author thus concluded that no proof was found that hypertension was the result of arteriosclerosis of the vessels of the medulla oblongata.

Studies on Microglial Cells.—According to the results of a preliminary series of experiments on cerebral embolism, through injections into the common carotids of 0.2 to 0.4 cc. of olive oil, undertaken by DADDI (*Le sperimentale*, 1931, 85, 5) with a view to studying the different elements of the nerve tissue in relation to the metabolism of fat, the author believes that he can establish as extremely probable, if not certain, the presence in the microglial cells of a fat-absorbing property which is completely analogous to that characteristic for the cells of the reticulum. The astrocyte seems also to possess the quality of taking up the fat actively, and further experiments will be made to establish this claim.

Oxychromatic Degeneration ("Intranuclear Inclusions") in Yellow Fever.—In this lengthy communication TORRES (*Mem. d. Instituto Oswaldo Cruz*, 1931, 25, 148) reports his examination of tissues from 122 monkeys infected with yellow fever and 17 human cases which died in the Rio epidemic of 1928. The inclusion phenomenon is regarded by the author as a specific degenerative process. He disputes the assertion of Cowdry and Kitchen that intranuclear inclusions are formed "of colony-like masses of individual particles about the size of rickettsiæ," and says typical inclusions consist of a groundwork of acidophilic nucleoproteins and a stroma of linin, both of which are normal constituents of the nucleus. The author describes various

types of inclusions found by him in his large collection of material; he attempts to trace a progression from early to end-stage forms. A marked difference between the inclusions of man and monkeys is recorded. Only 3 of his 17 human cases presented inclusions, whereas the incidence was almost 100 per cent in monkeys. Of the 3 positive human cases 2 died within 48 hours of the onset of the disease, from which the author infers that the presence of inclusions is synchronous with the presence of the virus in the blood of the patient. He says the virus of the Rio epidemic was a "weak inclusion former" in man but "strong" in monkeys. The author refers to the inclusion phenomenon as a necrosis which attacks only determined constituents of the nucleus, leaving the rest unaltered. He suggests the term "meronecrosis" (from *meros*, a part) as descriptive of the inclusion phenomenon in all the virus diseases.

The Effect of Prolonged Exposure of the Siliceous Spicules of a Fresh-water Sponge (*Spongilla Fragilis*) to the Action of Animal Tissues: A Contribution to the Pathogenesis of Silicosis in Man.—The spicules which MILLS (*Am. J. Hyg.*, 1931, 13, 224) recovered from fresh water sponges contained 18.3 per cent silicon dioxid. These the author injected intramuscularly into various animals, 7 in all. After varying periods ranging between 182 and 472 days the lesions were examined and the spicules recovered. The lesions were negligible, but the spicules were reduced in size indicating that they had undergone partial solution. In the case of 1 animal the spicules were injected into lung, where they remained 482 days. When the animal was killed a moderate degree of patchy fibrosis was found at the site of the injection. From these results the author states "This confirms the assumption held by many students of silicosis that particles of siliceous material are gradually converted into the colloidal state and as such exert a fibroplastic influence on the lungs of miners and other exposed industrial workers." The author does not give the size of the silica spicules he used, but from the photographs they seem to be about 0.3 mm. in length on the average. This is a dimension many times in excess of the common silica dust particle found in miner's lungs. The experiments lack controls and on the whole fail to convince one that the author has produced an experimental analogy of human silicosis.

The Rate and Site of Removal of Bacteria from the Blood in Blood Stream Infections.—OTTENBERG (*Arch. Path.*, 1931, 11, 766) showed, from the results of simultaneous blood cultures from both jugular veins and from an arm vein in cases of lateral sinus thrombosis, that there were always fewer bacteria in the arm vein than in the jugulars. In a series of control cases (bacterial endocarditis and sepsis) the colonies per cubic centimeter of blood were for practical purposes the same in all veins. The differences cannot be explained by dilution with the general circulation. The bacteria are evidently killed or are very rapidly filtered from the circulation. The actual site of filtration of the bacteria could not be proved, but the evidence that in a bacteremia the number of bacteria from an artery and that from a vein of an extremity are practically the same was offered to show that they were not removed by the peripheral tissues of the extremities. Other sites as lung and liver where

filtration probably largely occurs, are discussed. Reasons were given for believing that in many cases of sinus thrombosis bacteria were fed into the blood stream somewhat steadily over a period of time rather than in momentary "showers."

HYGIENE AND PUBLIC HEALTH

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Typhus Fever.—A Virus of the Typhus Type Derived from Fleas Collected from Wild Rats.—DYER, RUMREICH and BADGER (*Public Health Reports*, 1931, 46, 334) note that various investigators have suggested a vector for typhus in addition to the body louse which is held responsible for the disease in most parts of the world. In connection with their epidemiologic investigations in the city of Baltimore it was noted that there was a heavy infestation with rats in localities in which certain cases of typhus occurred. Fleas taken from these environments emulsified and injected into guinea pigs gave rise, after a suitable incubation period, to a febrile reaction not to be differentiated from that induced by typhus fever in the guinea pig. Monkeys had similar reactions and the blood of these animals developed agglutinins for the proteus organism that has proven so useful in the diagnosis of typhus in man. Rabbits gave similar results. Finally cross-immunity tests were made which indicated that the virus derived from fleas was not to be differentiated from that derived from human cases of endemic typhus of the new-world variety.

Transmission to the Third Generation of Antitoxin Derived by Active Immunization of the First Generation.—SUGG, RICHARDSON and NEILL (*J. Immunol.*, 1931, 20, 255) report an example of a guinea pig of the second generation transmitting to its own offspring (third generation) small amounts of antitoxin originally derived by active immunization of the first generation. Previous reports of failure of transmission were probably due to quantitative inadequacy of the immunity originally transmitted to the females of the second generation to persist to the time of birth of the third generation.

Excessive Ultraviolet Irradiation.—HESS and SMITH (*Am. J. Dis. Child.*, 1931, 41 775) state that in spite of the fact that ultraviolet irradiation has been made use of during the past 10 years or more to an increasing extent, no prolonged observations have been made on the effect of this remarkable remedial agent on the growth and functions

of the body. This is all the more remarkable, as from time to time the question has been raised as to whether these radiations may not inflict harm as well as be of advantage to the animal body. With this in mind, two series of rats were irradiated with the mercury-vapor lamp for a period of from 5 to 6 months or were given viosterol. Male as well as female animals were used; those in the first series were litter-mates, those in the second series, although not litter mates, were the progeny of the first. Three intensities of irradiation were given, mild, moderate and severe. The viosterol was given in small as well as in excessive amounts. The main object of the experiment was to note whether prolonged and intense irradiation or large doses of viosterol had a deleterious effect on the animals, as evinced by the rate of growth and by the size and appearance of the endocrine glands. The growth of the animals subjected to marked intensities of ultraviolet irradiation or given large amounts of viosterol was as good as that of animals which had lived under similar conditions but had not been subjected to irradiation or given viosterol. No difference was noted at necropsy between the endocrine glands of the treated and those of the untreated animals.

Significance of Positive Wassermann and Kahn Reactions in Leprosy.

—BADGER (*U. S. Pub. Health Rep.*, 1931, 46, 957) reviews the literature of the subject and presents the results of his own studies and summarizes his experience as follows: (1) There occurred an abnormally high incidence of positive serum reactions in the cases studied. (2) The positive reactions occurred nearly twice as frequently among the females as the males. (3) The positive reactions were more frequent among the patients under than those over 20 years of age. (4) Positive reactions were three times as frequent among the lepers as among a control group. (5) Definite changes in the serum reactions correlated with changes in the clinical manifestations of the leprosy were observed.

Rocky Mountain Spotted Fever (Eastern Type).—Transmission by the American Dog Tic (*Dermacentor variabilis*). DYER, BADGER and RUMREICH (*U. S. Pub. Health Rep.*, 1931, 46, 1403) recall that in a recent paper they had shown there prevails in the eastern part of the United States an infection of the Rocky Mountain spotted fever type with certain differences from the eastern type so far as lesions in animals are concerned, but immunologically identical. In the present paper they record the successful transmission of the eastern type of spotted fever by means of the common dog tick (*Dermacentor variabilis*). Details of the transmission and immunity tests are given together with the histopathology.

Prevalence of Undulant Fever in the United States.—HASSELLTINE (*U. S. Pub. Health Rep.*, 1931, 46, 1519) has studied the prevalence of undulant fever for 1929 and 1930. A total of 952 cases was reported for 1929 and 1387 for 1930, and it is indicated that these figures are too low to portray the actual prevalence of the infection. The disease seems to show the lowest incidence in the first quarter of the year with the highest in the third quarter.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 9, 1931

The Results of Direct Intrafollicular Injection of Extracts of Urine of Pregnancy.—MAURICE H. FRIEDMAN (from the Laboratory of Physiology, University of Pennsylvania). Although the biologic effects of urine of pregnancy are similar to those obtained with extracts of the anterior lobe of the pituitary, there has been no conclusive demonstration that the effective substances found in pregnant urine are derived from the pituitary. There are, indeed, many who believe that the action of urine of pregnancy is an indirect one, involving the stimulation of the pituitary in the injected animal. To determine whether or not extracts of urine of pregnancy were capable of exerting a direct effect on the ovary, a series of experiments were performed in which the follicles in one ovary of an estral rabbit were injected with minute quantities of an extract of urine of pregnancy. The other ovary in the animal was untouched. In 20 of 30 animals this procedure led to the formation of corpora lutea in the injected ovary, while the contralateral ovary showed no change whatsoever, presenting only large, unaltered follicles. In 6 control experiments physiologic saline was injected into the ovarian follicles instead of the urine extract, and in these instances no lutein tissue was developed. It is apparent, therefore, that extracts of urine of pregnancy when injected directly into an ovarian follicle may produce luteinization of the injected follicle in the absence of any general humoral change of sufficient magnitude to produce a change in uninjected follicles.

Anion Cation Studies in Liver and Gall-bladder Bile.—I. S. RAYDIN, C. S. JOHNSTON, C. RIEGEL and J. H. AUSTIN (from the Laboratories of Surgical Research and Research Medicine, University of Pennsylvania). In studies of the individual constituents of the bile subjected to gall-bladder activity in a bile-free gall bladder the total osmolar concentration tended to approach that of serum when sodium chloride was used. Solutions of calcium lactate were concentrated during day periods in the normal gall bladder although calcium was absorbed. Bile salts, either the glycocholate or taurocholate, were concentrated, although these studies could be conducted for only short periods because the bile salts caused a violent inflammation of the gall-bladder wall, which resulted in hemorrhage. Cholesterol in suspension was concentrated, and we found little if any evidence that it was absorbed. A mixture of the bile salts and a suspension of cholesterol was then studied. Bile salts were very slowly absorbed; cholesterol was not absorbed. The cholesterol did not precipitate out of the suspension as water was absorbed, as it did when a simple suspension was used, and the gall-bladder wall was not injured as early as it had been when bile salt alone was used.

We have studied the anion cation content of hepatic bile and the changes in the anion cation content when hepatic bile was subjected to gall-bladder activity.

The hepatic bile in known amounts was introduced into the bile-free gall bladder and permitted to remain there for from 2 to 24 hours. It was removed with a Luer syringe. Each animal was tested at the time of operation in order to be sure that we could recover the amount of fluid introduced. After catheterization and washing of the gall bladder normal saline solution was left in to test the absorptive function of the viscus and to ascertain whether accessory ducts had been overlooked. As long as the gall bladder remained normal fluid was absorbed. The exact amount varied considerably. Estimations of the pigment concentrations in hepatic bile subjected to gall-bladder activity have shown increases in concentration of this substance over a 24-hour period, varying from 5 to 17 times that of the bile introduced. The minimum figure is in agreement with the low figures published by Rous and McMaster, but the maximum figures are considerably higher than their figures.

Hepatic bile is more variable in its electrolyte composition than is serum. This is true for different animals and for the same animal at different times. It is higher in base, total anion and, as a rule, in bicarbonate, while chloride tends to be somewhat lower than that of serum. The bile salt concentration has varied from 15.6 to 66 mille equivalents per liter. The calcium content of hepatic bile is nearly always higher than that of serum and is much more variable. The pH has varied from 7.1 to 8.6. A comparison of the estimated anion cation content of hepatic bile shows that unknown anions account for a median of about 12 mille equivalents per liter.

The amount of anion which might be accounted for by the small protein content of hepatic bile is not more than a few mille equivalents per liter. The amount bound by phosphoric acid either inorganic or in lipid combination, by fatty acids or by bile pigments, is unknown.

After subjecting a single injection of hepatic bile to gall-bladder activity for a short period, one finds considerable variability in the composition of the bile. In 7 of the 9 instances where complete studies were made the per cent decrease of the total estimated anion was greater than that of the cation. In the remaining 2 experiments anion and cation showed the same per cent decrease.

An analysis of our data shows that bile salt and undetermined anion increase in concentration. In the 2 experiments where bile salt concentration increased above 40 per cent the total base concentration increased. If the gall bladder is constantly receiving bile and the bile salt and undetermined anion concentrations are increasing the retained base will also increase in concentration. We have obtained a bile salt concentration as high as 194 mille equivalents per liter from a single injection of hepatic bile. The exact time at which base concentration will increase will depend upon the rapidity with which the bile salt undetermined anion concentration increases.

The composition of the bile after stay in the gall bladder is the resultant of an absorption of water, accompanied by some bile salts and a disproportionately high absorption of chloride and bicarbonate. The exact change in the known anions perhaps bears some relation to the increase in concentration of the bile salts and unknown anions.

The change in pH is probably dependent on an increase in concentration of some unknown acid. The variability in the composition of the bile removed from the gall bladder is to be attributed to the fact that we are dealing with a resultant of different rates of absorption of the various components rather than with a condition of equilibrium. When bile is constantly added to the amount in the gall bladder, base undoubtedly rises.

On Osmotic Properties of Living Cell Fragments.—BALDUIN LUCKÉ (from the Laboratory of Pathology, University of Pennsylvania). It is well known that the normal living cell acts as if it possessed a semi-permeable membrane; that is to say, a protoplasmic layer which, while permeable to water, is more or less impermeable to many dissolved substances. Upon this conception are based the majority of the theories of selective permeability and of osmotic behavior of cells.

Little is known about the properties of reconstructed membranes, *i. e.*, membranes that have in some sense been reformed. It is known that when a cell is mechanically injured, by tearing, cutting or crushing, a new surface film will form almost instantaneously (at least under favorable conditions) over the injured surface or over the protoplasm which has been extruded. Such newly formed films have the same selective permeability with respect to various dyes as has the whole cell.

The technique lately developed by E. N. Harvey of dividing spherical cells (unfertilized eggs of the sea urchin) into two nearly equal spheres by means of centrifugation in a medium of proper density, affords an opportunity of studying the properties of reconstructed surface membranes of cell fragments that have suffered no injury, for upon insemination these fragments form fertilization membranes and subsequently undergo cleavage. Since division of a sphere considerably increases surface area, the surface of the newly formed fragments must in some sense be a reconstructed one. The question we wish to answer is, do such reconstructed membranes have the same properties of semi-permeability as the whole cell?

One of the best methods for studying semipermeability of cells is the osmotic method. With suitable cells, in this case the living unfertilized eggs of the sea urchin, it has been shown that their volume changes in anisotonic solutions are adequately accounted for by the law of Boyle-van't Hoff, which relates the volume of a closed osmotic system to the osmotic pressure of the surrounding medium with which it is in equilibrium. Stated alternatively, we have previously found that with this material the product of volume and pressure is approximately constant, if correction is made for volume occupied by osmotically inactive material. From these results the inference may be drawn that the semipermeability of the cell surface is nearly perfect. If the law of Boyle-van't Hoff should also hold for cell fragments it would indicate that their surfaces were similar to those of the original cells. That this law does hold was shown by measuring the volume of the cell fragments in three different concentrations of sea water with which they had been brought in osmotic equilibrium. Further proof of the semipermeability of the surface was obtained by measuring previously swollen cells after they had again attained equilibrium in ordinary sea water. It was found that the fragments returned to within 2 per cent of their

original size. From these experiments it is concluded that the reconstructed surface of living cell fragments is similar to that of the original cell; that it is an approximately semipermeable one.

Arteriovenous Anastomoses.—E. R. CLARK, E. L. CLARK and E. A. SWENSON (from the Department of Anatomy, University of Pennsylvania). Direct connections between arteries and veins, by passages decidedly larger than capillaries, which have been called arteriovenous anastomoses, have been described by Sucquet (1862), Hyett (1864), Hoyer (1877), Pourceret (1885), Grosser (1902) and Grant (1930). There is general agreement that they exist normally in the erectile tissue of the sex organs, in the balls and nail beds of fingers and toes, in the tip of the nose, the tip of the tail and in the outer ears of various mammals. While they have been described in other locations, their existence elsewhere has not been established. The best descriptions of them, made upon injected and fixed material, are those of Hoyer and Grosser. According to them, arteriovenous anastomoses are quite definite structures, ranging in inside diameter from 10 to 50 micra (except for one in the tip of the bat's wing, which may reach a diameter of 150 micra) with a wall which greatly exceeds in thickness that of the arteriole which precedes it. The smooth muscle has, in addition to the usual circular arrangement, an inner longitudinal layer and an outer layer of oblique cells.

Grant (1930), whose studies have paralleled our own, has made interesting observations on arteriovenous anastomoses in the rabbit's ear as seen through the intact skin, and has described their behavior under a variety of experimental conditions. He considers that they play an important rôle in temperature regulation in the rabbit's ear and the tip of the human finger.

Our attention was called to them first in the fall of 1929, when we saw them in the type of transparent chambers introduced in the rabbit's ear in which the preformed tissue is retained, with its original vessels and nerves. They were made accessible to microscopic study by the removal of the cartilage and the skin of the inner side of the ear, and the substitution of a thin sheet of mica. These structures were demonstrated in the living animal at the meeting of the American Association of Anatomists at the University of Virginia, in April, 1930, and at the International Congress of Anatomists in Amsterdam, in August of that year.

Studies of these interesting structures have only begun, but already many suggestive observations have been made, while the possibilities for the study not only of their function but also of the factors responsible for their formation seem to be unlimited, with the methods for bringing them under observation in the transparent double-walled chambers. It was found that arteriovenous anastomoses are normally present in the rabbit's ear to the extent of from 40 to 50 in an area approximately 1 cm. in diameter, and the special preparation enabled the observer to make precise observations upon their normal behavior as well as their behavior under experimental conditions for many hours a day, and for weeks and months. It was found that they are definite and, certainly in most cases, permanent structures. Some of them are straight and some are twisted or coiled. They may occur singly or in groups of 2 to 8. They possess a thick wall which suddenly thins to

a single endothelial, noncontractile layer at the venous end which always remains wide, giving a funnel-shaped appearance.

In behavior it has been noted that they are extraordinarily contractile, the most contractile of all the parts of the peripheral vascular system in the ear. The arteries and arterioles of the ear undergo frequent spontaneous active contractions, usually showing a periodicity of two or three contractions per minute. These general contractions usually involve also the arteriovenous anastomoses. But between such contractions there may be separate contractions of some arteriovenous anastomoses, and it is not uncommon to see an individual arteriovenous anastomosis remain contracted for hours or even days, while a neighboring one may be showing four to eight alternate contractions and dilations per minute. The arteriovenous anastomoses contract simultaneously with all the peripheral arteries and arterioles following stimulation of the whole animal.

In addition to the study of arteriovenous anastomoses in the preformed tissue, it has been possible to observe the new formation of definite and permanent ones in new tissue which has grown into an empty space left between the mica and a kodaloid table in a second type of transparent chamber, which we have called the "round table" chamber. In 1 such specimen installed in July, 1930, taken to Amsterdam for demonstration and brought back to America, four arteriovenous anastomoses were observed in October, 1930. They were watched for several months and during that time showed no evidence of nerve-controlled contraction. In March, 1931, 8 months after installation, one of the four showed definite contractions which synchronized with the contractions of the main arteries of the ear. In June, 1931, at 11 months, two others showed similar synchronized contractions. At that time, and in July, the fourth one still failed to show synchronized contraction.

It was possible to obtain motion pictures of these four arteriovenous anastomoses, of one of them in March, 1931, and of all four in June, as well as motion pictures of similar structures in a second rabbit in a chamber installed and cared for by Dr. R. O. Rex in our laboratory. (A reel of motion pictures showing both contracting and noncontracting arteriovenous anastomoses was shown.)

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ORIGINAL ARTICLES.

PULMONARY FIBROSIS: EXPERIMENTS OF SHORT DURATION.*

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It has been known for at least 4 centuries that men who inhale the dusty air resulting from certain industries suffer severely from respiratory disease, especially from tuberculosis. Heffernan, in considering the peculiar behavior of tuberculosis when associated with silicosis, wrote: "The total absence of conjugal infection among the wives and widows of the silicotic cases is on all fours with the oft-quoted observation of George Bauer, who wrote in 1557 that women could be found in the mining communities of the Carpathian mountains who had been widowed six times over by miner's phthisis." Throughout the present century investigations have been carried on in all the industrial centers of the world. It has been shown that the hazard of dusty atmosphere is pulmonary fibrosis and that different dusts possess different powers to excite and produce scarring within the lung. Silica is by far the most potent agent in the causation of silicosis and it has often been said that fibrosis of the lung is brought about "by any given dust so far only as this dust contains silica" (Riddell). Bohrod recalled that

* Read before the meeting of the Minnesota Society of Internal Medicine, Minneapolis, April 13, 1931.

siderosis was the first form of pneumoconiosis to be described, and attributed the description to Zenker, who, in 1867, described 2 cases of what he termed siderosis. He proposed for the whole group of diseases caused by dust the term pneumoconiosis. Klotz, in 1914, showed that pneumoconiosis could be produced by inhaled particles of carbon, and that a severe type of fibrosis might be produced. The fibrosis was of the same type as that produced by silica, but required a longer time for its production.

The variations in the time required by atmospheres containing dust of known and constant nature, but of different concentrations, to produce fibrosis in the person employed, has led to a systematic study of industrial hazard. It was found that not only does silica cause a specific lesion, but that factors such as infection, size of dust particles, chemical reactions in tissue, solubility of dust particles, moisture, hygienic environment of the men, races of men, nationality, and interruption of work, all played parts in the production of the fibrotic lesion or influenced its progress or its prognosis.

It has been proved⁴ that there are certain limitations of permissible dustiness in the dangerous trades, and the figure that has been more or less arbitrarily chosen is 10,000,000 particles for each cubic foot of air. Observers have shown that the injury produced is in direct ratio to the numbers of dust particles and that, if this number is more than 20,000,000 particles for each cubic foot of air, the risk of the development of fibrosis and of its most important and most common complication, tuberculosis, grows into a really serious menace. It is assumed, in any statement of this kind, that not only the percentage of silicon is high but also that from 50 to 70 per cent of the particles of dust are smaller than 10 microns in diameter. In men examined in The Mayo Clinic who had been subjected to dusty atmospheres, the length of time required for the breakdown of the protective mechanism, and the consequent production of fibrosis, varied, except in exceptional cases, over the wide limits of at least 5 to 15 years, depending on many physical, chemical and bacterial factors. Furthermore, experiments on animals subjected to a dusty atmosphere have almost uniformly failed to produce a condition comparable to the fibrosis of silicosis.¹ For these reasons, study of the mechanism of the production of this pathologic state becomes at once very difficult. In man, the end results of fibrosis and of tuberculosis have been thoroughly studied, and the clinico-pathologic picture has been well described. Less exact information is available regarding the pathologic processes, from the earliest evidence of failure of the protective forces to rid the lung of its load of dust, to the full development of the protective mechanism that attempts to dissolve, destroy, remove or mobilize the irritant and encapsulate it, resulting in the production of the dense fibrosis of the silicotic lung.

Landis⁹ wrote: "The solution, I think, lies in the fact that the

area is at first protected by the cilia of the outer respiratory tract. Gradually these defenses break down and the small particles of dust are taken up by the lymphatics and appear in the alveolar cells, the first histologic change noted being the swollen alveolar cells. Other changes are marked swelling of the cells lining the alveoli, with marked pigmentation in the alveolar walls in and about the bronchial walls. Deposits of dust seem to localize at the junction of the lymphatic channels. The cut surface will show this in the gray parenchyma of the lung. This represents the stage of pneumoconiosis, and with the definite deposits of these small points of dust one begins having a marked inflammatory condition of fibrous tissue. The fibrous tissue and the dust alternate, the points coalesce and ultimately there is a large fibrous mass."

Experiments done in 1925¹⁰ on the aspiration of particulate matter into the lung, proved that the technique then employed permitted particles of very small dimension, comparable to the particles of silica that effect the pulmonary changes in cases of silicosis, to reach the alveoli, alveolar walls, and subpleural spaces, within a period of 40 minutes. By this simple technique, therefore, we were able to circumvent the experiments of long duration, in which dusting had been employed, and which had failed because of the protective mechanism that rids the lung of foreign particles and that does not permit them to reach the finer bronchioles or the alveoli. It is the material that cannot be removed from the lung that does the mischief, not the material which soon after entrance is removed from the lungs. By administering the foreign material in the form of a suspension, the primary mechanism of removal was at once overcome, and the particles were placed so deep in the bronchi and the alveoli that the secondary process of protection of the lung from injury was promptly mobilized and started into activity. This mechanism was defined by Maximow as follows: "All multicellular organisms are endowed with the ability to repair damages inflicted by extraneous factors and autogenous disturbances to resist, neutralize, digest or destroy noxious agents which endanger the normal course of life and to eliminate them. The connective tissue, the so-called 'mesenchyme' plays the predominant rôle in these defense reactions."

The worker in the dusty atmosphere of the dangerous trades is unharmed as long as the dust can be satisfactorily removed by the cilia of the outer part of the respiratory tract, and he becomes injured when that mechanism of protection breaks down and dust reaches the alveoli. It was possible to produce, within a brief period, comparable loss of competency in the normal defense mechanism in an animal. For these reasons it was thought probable that the endowment to repair, resist, neutralize, digest, or destroy might be studied, and that the facts obtained might be used to explain the production in man of silicosis.

Experiments. In the first experiment the dog lay on an inclined plane with the head of the table elevated 10 cm. higher than the foot. The head was held to one side. Forty cubic centimeters of a mixture of 20 per cent barium and India ink was given in doses of 5 cc. every 5 minutes. It was simply dripped into the mouth and allowed to flow down the cheek. The dog was kept anesthetized with ether throughout the experiment, and the suction of inspiration was the only force employed to transport the suspension of particles down to, and through, the trachea into the lungs.

At the conclusion of the experiment the dog was despatched by overetherization, and necropsy was done at once. When the trachea was opened, mucus that was stained black could be seen within the trachea. It extended downward, past the carina, into both main bronchi, and the major portion entered the lower lobes of the lungs. More found its way into the right side than into the left and only small amounts were transported into the upper lobes. Within the lower lobes, the mucus, laden with particulate matter, passed so deeply into the bronchial divisions that the bronchi were too small to allow the finest scissor points to be inserted into their lumens for further opening of their walls. However, by gentle traction, tenacious threads of mucus, blackened by India ink, could be extracted.

The cut surface of the lung, in its distal parts, was mottled with tiny black spots which represented the finer bronchial divisions. In many instances these were removed, in part by cohesion and traction, and by this means could be distinguished from any possible effect of anthracosis. The pleural surface was mottled with blackened areas which were separated from each other by visceral pleura of normal color.

Microscopically there was no possible confusion between the anthracosis normally present and the pigment artificially introduced. The former presented the characteristic appearance. The granules of carbon were intensely black and were so densely packed within cells that the nature of the phagocytic cell could not be determined. These were grouped in the characteristic fashion about bloodvessels and bronchi and served to identify the presence of the small bronchioles. Carbon was not found in the alveolar walls, but a linear distribution could be seen in the subpleural spaces. This description is similar to that of the lymphatic system of the lungs and pleura.^{2,6,12} It is in the lymphatic spaces and tissues that impounded particulate matter is stored. It is impounded and stored when the lymphatic system fails in its function of removing fluid, and especially in its function of removing particulate matter.

The appearance, after the artificial introduction of foreign matter, was decidedly different from that of anthracosis. The suspension of barium, 20 per cent, colored with India ink, was chosen because the particles were many times smaller than blood cells, because

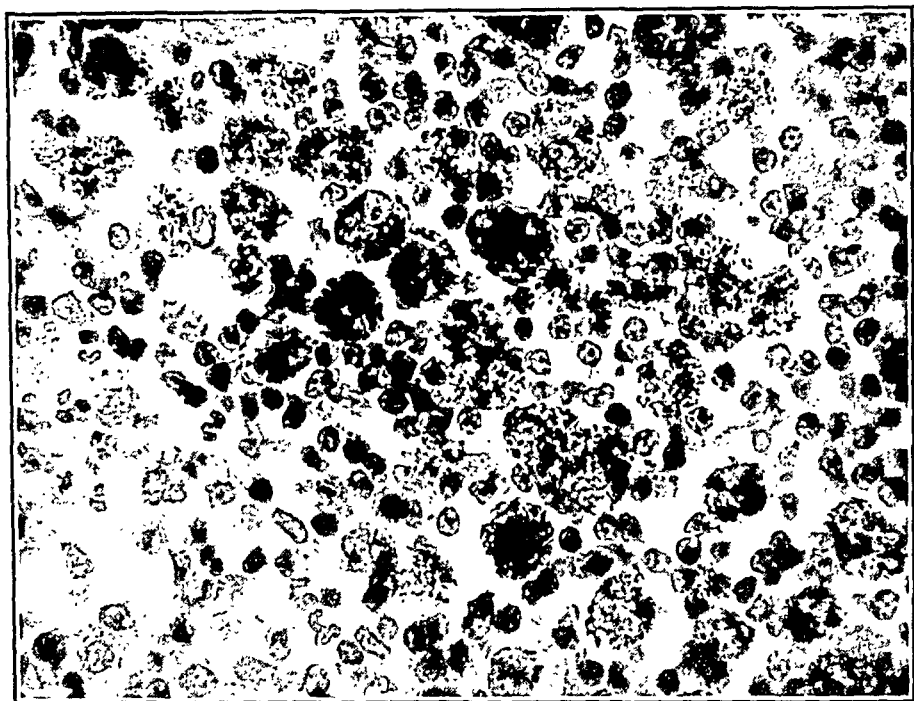


FIG. 1.—Nongranular mononuclear phagocytic cells known as histiocytes, clasmacocytes or polyblasts. The cells show marked evidence of phagocytosis; they are from trabeculae of a peritracheal lymph node and reached the node one and a half hours after intratracheal administration of particulate graphite.

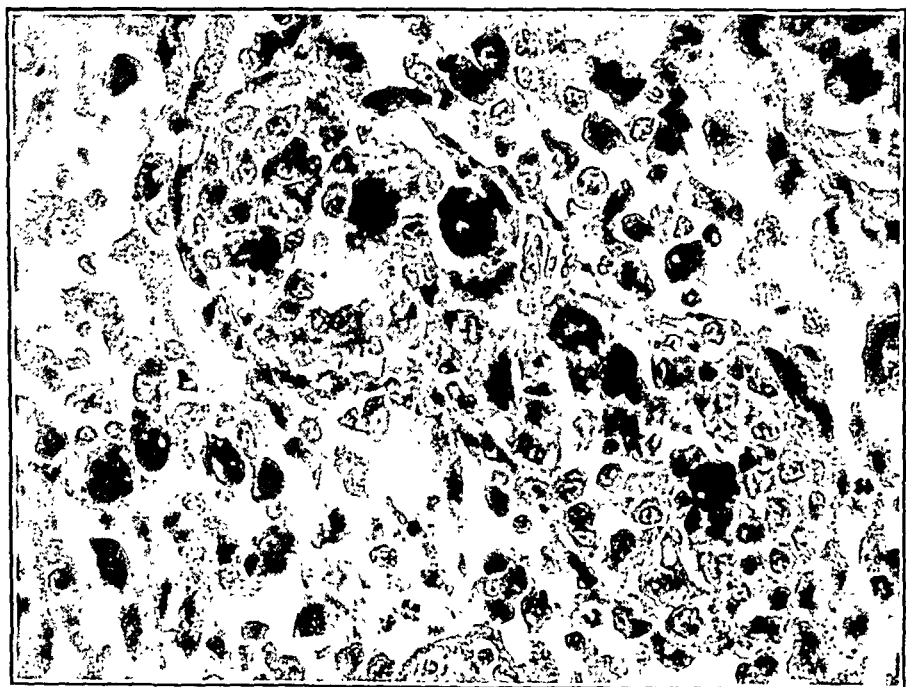


FIG. 2.—Peritracheal lymph node after absorption of colloidal iron from the lung. The node is filled with phagocytic cells containing iron. Littoral cells are filled with iron; evidence of early fibroplastic action.

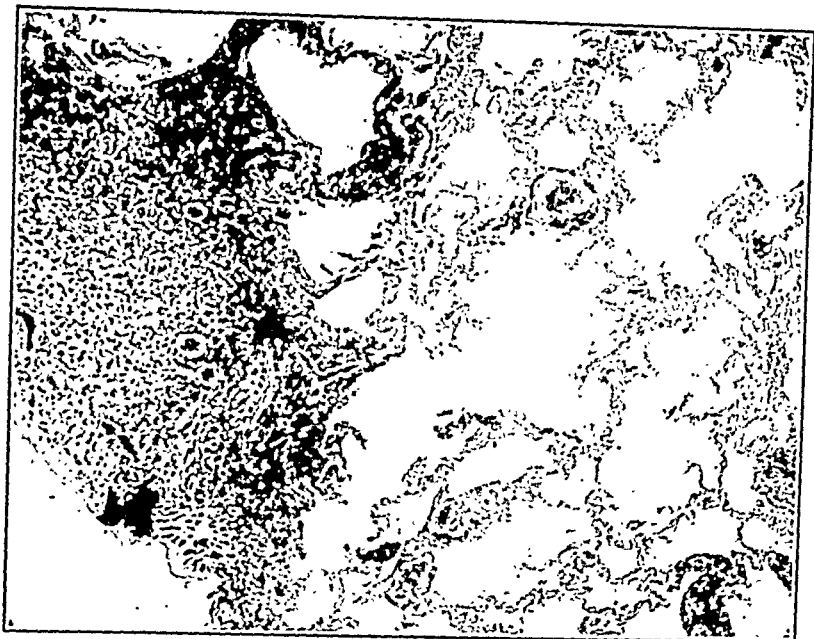


FIG. 3.—Tissue from lung of human being, with a localized subpleural fibrous tissue plaque, in a case of anthracosis. Storage of carbon has taken place in perivascular and perilymphatic spaces. There is evidence of slight reaction in the alveolar walls, emphysema.



FIG. 4.—Tissue from lung of a quartz miner. Dense fibrous tissue is present. The alveolar walls are markedly thickened and the contained capillaries are compressed. The cells lining the alveoli are cuboidal and desquamation of them has taken place, giving rise to the so-called dust cells, which permit of continuous evacuation of silicon from the lung. The fibrosis extends throughout the parenchyma, far removed from the perivascular and peribronchial lymph depots. There is a high degree of emphysema.

microscopically they were much lighter in color than the carbon seen in anthracosis, and because the two could not readily be confused. On studying the sections, it became apparent that within 40 minutes the force of aspiration had carried foreign material from the mouth into the bronchial tree and into the alveoli, and thence a migration had occurred which transported the particles into the alveolar walls and to the periphery of the lung, in which, beneath the superficial layer of the pleura, the India ink and barium could be identified.

Within the hour taken to perform the experiment, particulate matter had been placed as deeply in the lung as any dusting experiment could have placed it in months, and probably as deeply as man would have inhaled it after even years of exposure to an atmosphere heavy with the dusts considered dangerous in industry. We were thus permitted, by overcoming the first protection afforded by the cilia of the upper part of the respiratory tract, to see the first stage of the second protective mechanism, which is called into service when dusts can no longer be removed by ciliary transportation of dust-laden mucus.

The second stage of protection depends on the ability of the lung to repair injury after the first mechanism has been overcome. Then the defense reaction is taken up by the mesenchyme, and the offending foreign bodies are destroyed or removed from the organ through the lymphatic structures, or are stored in depots where they are so invested that they do the minimal amount of harm. The process is, first of all, one of phagocytosis; later, one of lymphatic drainage and, finally, one of fibrosis to encapsulate what cannot be removed.

Much of this second protective mechanism is not thoroughly explained. We believe that the part played within the lung by the mesenchyme is as follows:

The exact origin of the phagocytic cells of the lungs is still in question. Hitherto they were thought to be of endothelial origin. This was at the time the endothelial origin of phagocytes in general was accepted. Since this general hypothesis has been dethroned, concepts of the origin of the phagocytic cells in the lung have changed. The present concept is essentially that they are derived from the mesenchyme. It is thought that these cells arise from primitive mesenchyme cells which lie within the interalveolar septums and increase in number as the demand arises. The changes in our concept concerning the origin of the phagocytic cells in the lung coincide essentially with the changes in our belief regarding the morphology of the alveolar cells. In fetal life the alveolus is lined with a cuboidal type of epithelium. Subsequently this epithelium is lost and the alveoli then come to be lined by a flattened layer of cells which are now said to be derived from the mesenchyme. The exact fate of the original embryonic epithelium is not known. The mature alveolar cells of mesenchymal origin are potential his-

tiocytes, so that as the occasion demands, these cells may enter the lumen of the alveolus and phagocytose débris or foreign particles. These lining histiocytes are probably identical with the cells that lie within the septums; therefore as a shedding of lining histiocytes occurs, other histiocytes, from the septums, take their place. These cells, as they enter the lumen of the alveolus, phagocytose foreign particles, pass back through the wall of the alveolus or the bronchiole into the substance of the lung, and either migrate directly through the parenchyma, or enter lymph tracts and proceed to the regional lymph nodes.

In this respect, then, we may say that alveolar phagocytes, or the pulmonary dust cell, or the so-called heart failure cells, are nothing more or less than normal histiocytes, comparable in every way to those which abound throughout the body generally. They are derived from the mesenchyme, may migrate freely through the pulmonary parenchyma, and are concerned functionally with the defense mechanism of the organ.

In our experiment we were able to demonstrate particulate material in the farthest reaches of the lung. When microscopic slides were prepared and examined, the mechanism of migration from the air tubes into the parenchyma of the lung became apparent.

Aspirated material could readily be distinguished in the smallest bronchial divisions. It was mainly in a free state, but mononuclear phagocytic cells could be seen scattered through it; these were invariably loaded with particles. In some instances the foreign particles were literally packed in the cell in such amounts that the identity of the cell itself became difficult to determine. The same type of phagocytic cell was seen within the alveoli and in the alveolar walls, and their migration could be followed as far as the subpleural spaces, in which they were sometimes arranged in a linear fashion, suggesting their inclusion in lymphatic spaces. Particles in a free state were also found in the alveolar walls. Presumably they had penetrated the alveolar lining and presumably also they later were engulfed by phagocytic cells of mesenchymal origin known under different names, histiocytes, clasmatocytes and polyblasts.

Curiously enough, there was little evidence that polymorphonuclear leukocytes had migrated from the bloodvessels. Ordinarily we have learned to expect them to be the first phagocytes seen in inflammation produced by the introduction of sterile particulate material. The usual influences of attraction, whether chemotactic, osmotic, or electrotropic, enumerated by Maximow, failed to introduce these cells and permit them to take on themselves the first burden of phagocytosis. In our experiments⁶ dealing with pleural exudation, polymorphonuclear leukocytes were the first phagocytes to appear, and as they withdrew from the exudate, or disintegrated, monuclear cells of polyblastic type, which we have

called clasmatoocytes, appeared later and continued the phagocytic function.

The phagocytosis under discussion was, however, essentially confined to mononuclear cells, identical in appearance with the clasmatoocytes we have described in our work with pleural exudates.⁶

In the second experiment a half-grown puppy that had lived in the country was chosen so that all risk might be obviated regarding the confusion of foreign particles artificially introduced with those present in an anthracotic lung. A colloidal suspension of graphite was introduced into the trachea, and 1½ hours later necropsy was performed. The lower lobes of the lung had received almost the whole amount of the suspension of graphite. A few small regions of infiltration occurred in the upper lobes. These portions of the lung into which the graphite had been aspirated were swollen, edematous, and black. Examination of the gross specimen disclosed that the graphite had filled the entire bronchial tree. Examination of microscopic slides revealed that the same mechanism of mononuclear phagocytosis had operated in this animal as in the first, to carry the particulate matter throughout the pulmonary parenchyma and to the subpleural spaces. Polymorphonuclear leukocytes were seen in relatively small numbers, but they were definitely phagocytic in action.

Moreover, a further phenomenon in protective processes appeared. There were indefinite, blackened lines in the visceral pleura, that were densest at the hilum of the lungs, and the tracheobronchial lymph nodes were enlarged and very densely blackened. This mechanism for removal of obnoxious particles was entirely confined to the lymphatic system. The bloodvessels did not contain phagocytic cells which had engulfed particles of pigment. The lymphatic system had evidently begun functioning early, because, even after 1½ hours, the graphite had not only reached the tracheobronchial nodes, but had blackened the paratracheal nodes. The node commonly found in the dog opposite the first rib was deeply blackened. It is only a short distance removed from the confluence of its efferent lymph vessels and the venous system.

Fixed sections of the inferior tracheobronchial nodes, of the superior tracheobronchial nodes and of the paratracheal lymph nodes, were examined microscopically. The central portion of the glands, mainly the trabeculae, were seen, on low-power examination, to be filled with graphite. On increasing the power of magnification, the graphite was found to be entirely phagocytosed, mainly in markedly enlarged nongranular mononuclear cells; a few polymorphonuclear leukocytes took part in the phagocytic action and were loaded with particles of graphite. It was apparent that the mesenchyme had taken on itself the function of protection.

After phagocytosis had occurred, the lymphatics had rapidly conveyed the cells, with their debris, out of the lung. Within

1½ hours these were as far removed as the farthest lymph node in the lymphatic system leading to the lymphatic-venous juncture.

All of the bloodvessels of the lung and the nodes were free of pigment and of pigment-bearing cells.

The liver had felt the influence of irritation from foreign bodies. Kupffer cells were enlarged and swollen, showing evidence of histiocytic activity.

Comment. In our other experiments,⁷ in which the tracheo-bronchial and the paratracheal glands have become filled with absorbed material from the pleural space, a similar reaction occurred in the reticulo-endothelial system, especially of the liver. The Kupffer cells became enlarged and bulged into the sinusoids. The reaction seemed to be one of stimulation due to the influence of foreign material, and always preceded the phagocytic phenomenon which occurred after the lymph stream had commingled with the blood. Then débris and particles were ingested by the Kupffer cells. The final disposal of particles engulfed by the Kupffer cells is not known. Presumably the Kupffer cell itself is transformed into a fibroblast or is destroyed.

When the conveying mechanism fails and débris cannot be carried out of the lung, Nature stores it in convenient depots and sets about to make it harmless. Since the whole process of removal is carried on by the lymphatic system, it is obvious that the storage should be within that system. Therefore the walls of the bronchi, to their finest divisions, the ductuli alveolares, have their lymphatic spaces crowded with unremoved cells containing intracellular particles. The lymphatic tissue at the bronchial divisions, and the lymph vessels surrounding the arteries and veins, all bear their load of phagocytic mononuclear cells filled with débris, and the subpleural lymph channels are similarly filled.

The first step toward the formation of fibrous tissue, and the last toward protection, is now ready to start. We have found that fibrosis began early in the mediastinal tissues which had taken within themselves the graphite-laden phagocytic cells of pleural exudates. We noted that the polymorphonuclear leukocytes, which had reacted first as phagocytic cells, broke down or disappeared, and that the mesenchyme cell, the clasmatocyte or histiocyte, or resting wandering cell, or mononuclear exudate cell, or polyblast of Maximow, increased in numbers as time elapsed. These are all names of the same cell in different states of activity. They seemed most active in removing the cause of the inflammatory irritation and clearing the tissue of débris. They were not only in large numbers, but they were densely crowded with particles, and did not appear to degenerate and break down readily. By the fifth day, they seemed to elongate and form fibers, and seemed actually to become transformed into cells resembling fibroblasts. The fixed tissue cells, or fibroblasts, were rarely phagocytic and reacted slowly, becoming

enlarged as did the Kupffer cells in the liver, and proliferated. Together, these transformed clasmatoocytes and fibroblasts became part of granulation tissue which later developed into true scar tissue.

A similar process occurs within the lung. The degree of fibrosis, however, is dependent on the nature of the phagocytosed irritant, and explains the difference in the amount of fibrosis seen in the lungs of workers in soft coal and those who have spent a much briefer time in a much less dusty atmosphere of the quartz mine. Up to the stage of fibrosis, the mechanism is the same. The fibroblasts provide a fibrous capsule which invests the irritant substance that remains, as yet intracellular, and when the irritation is prolonged or continuous they proliferate to such a degree that actual induration occurs. It seems probable that the phagocytic cell elaborates some substance that attempts to destroy or liquefy its load of debris. Maximow expressed the belief that this may be an enzyme or other soluble substance. It is at this point that bacterial, mechanical or chemical differences in the ingested material control the degree of succeeding fibrosis. Gye and Kettle have attempted to explain why silica is conspicuous and is possibly alone among common dusts in its capability of inducing extreme degrees of fibrosis. They wrote: "The view most often expressed is that silica owes its injurious quality to its physical properties. Moore tabulates the properties as follows: (1) Its heaviness; (2) its sharp, vitreous fractures, and (3) its great hardness and insolubility. Hardness, heaviness and sharpness of points or edges are properties which lose their significance when applied to particles of dust enclosed in the cytoplasm of wandering cells; direct mechanical injury to the lung (under the circumstances by which the dust gains access) is almost inconceivable. The property of insolubility deserves more attention. Silica, though insoluble in all acids, except hydrofluoric, is readily dissolved in alkalis. The statement, therefore, that silica dust is insoluble is only partially true, and the conditions under which a solution may be obtained are relevant to the problem of silicosis. Carbon particles, certainly in a test tube, are more insoluble than silica particles, and it is universally agreed that carbon dust, unless in large amounts, is of no pathologic importance. In silicosis the injury to the lungs is a continuous process, and the amount of fibrous tissue formed is much greater than can be explained upon the mechanical process involving disturbances of microscopic anatomic relationships. Further, the fibrosis extends far beyond the near neighborhood of the silica particles." In the report of the committee on silicosis presented to the Industrial Hygiene Section of the American Public Health Association, Minneapolis, Minn., October 4, 1929, a similar view is expressed:

"According to Heffernan on the biophysics of silica and etiology of silicosis, the disease is the result of the local action of hydrated silica upon pulmonary tissues; the action is physico-chemical in

nature and its development depends upon the rapidity with which fresh silica hydrosol is brought into contact with pulmonary tissue; substances such as alkalis, which favor the formation of silica hydrosol from silica, when added to silica dust accelerate the development of silicosis; and substances such as carbon coal dust or clays, which retard or prevent the formation of hydrosol from silica or which coagulate the hydrosol when formed, retard or prevent silicosis."

A more recent communication regarding the chemical reaction of silica on the tissues has been made by Mills. As a result of his investigations on *Spongilla fragilis* he concluded: "The spicules of the fresh-water sponge, *Spongilla fragilis*, are composed of opal, a form of hydrated silica, which is similar to quartz in its chemical reactions. These spicules, when introduced into the tissues of animals, are slowly but definitely dissolved, proving conclusively that silica is soluble in the tissue fluids of animals, and presumably of man. This confirmed the assumption held by many students of silicosis that particles of siliceous material are gradually converted into the colloidal state and as such exert a fibroplastic influence on the lungs of miners and other exposed industrial workers. Definite fibrosis of the lung of a dog into which the spicules had been introduced suggests that there is a concomitant injury attributable to the disappearance by solution of the siliceous elements of the spicules."

It seems probable, then, that the final process is a chemical one which occurs within the cell. The "enzyme," or soluble substance elaborated by the phagocyte, fails to dissolve the particle of carbon, which is therefore bland and nontoxic, and can be stored without destructive tissue reaction appearing, and stimulating continuous hyperplasia of fibroblasts and late transformation into scar tissue. The phagocyte, by the chemical action of its elaborated substance or enzyme, seems, however, to produce a tissue poison from the particles of silica, and this process continues as long as silica remains in the lung. It is slow but continuous and stimulates constant hyperplasia of fibroblasts and constant addition to the amount of scar tissue. It is the explanation of the fact that men may lose respiratory competency years after having been engaged in work which is done in a dusty atmosphere, in which there is a high percentage of silica.

The specificity of silica, therefore, seems to be due to its transformation within the cell from inert particles to a substance that is a protoplasmic poison. Gye and Kettle have expressed their view as follows: "Our work has been based on the known facts: (1) That colloidal silica is a cell poison; (2) that colloidal silica is the most easily formed soluble form of silica, the circulation of silica in nature depending on this, and (3) that living matter (soil bacteria) is able to break up mineral silicates with the formation of

soluble silica. We judged it probable that the fibrosis brought about by finely divided silica was due to the slow formation in the tissues of silica sol, either directly or through the intermediate formation of sodium silicate, which is decomposed by carbonic acid, the solution formed acting as a cell poison."

It is probable that other inorganic substances may produce protoplasmic poisons when chemical reactions occur within the cells. We have in progress at present experiments in which we are using colloidal iron in a similar way to that described in the protocol of the experiment in which graphite and India ink were employed. Within 12 days we have observed early but widespread and definite fibrosis in the lung.

The Kupffer cells of the liver, the littoral cells of the paratracheal lymph nodes, the cells of the tubules of the kidney and of the cortex of the suprarenal glands all contained iron. There was, also, definite evidence of injury to the cytoplasm, both in the lymph nodes and in the liver.

Conclusions. It seems probable that the fibrosis of the lungs produced in workers exposed to dusty atmospheres, especially those in which fine particles of silica make up the larger percentage of the dust, is an end product and represents a progressive defeat of the protective mechanisms of the body. It is never found until the lung fails to rid itself of dust carried out of the bronchi by ciliary action or of dust carried through the lung by way of the lymphatic channels. With the breakdown in the carrying mechanisms, the burden of protection is the phagocytic cell, which, with its load of engulfed material, passes to all parts of the lung and ultimately becomes immobilized in those portions of parenchyma in which lymphatic tissue is abundant. The cells concerned are polymorphonuclear leukocytes, which are the first to appear, to disintegrate and to disappear, and clasmatoocytes, which appear later, are extremely active, break up less readily, and may become transformed into fibroblasts. In association with the tissue fibroblasts the clasmatoocytes form scar tissue.

Finally, fibrosis is the result of the action of substances secreted by the cell on the foreign particles. If a tissue poison results from this chemical action, fibrosis is encouraged, and is progressive, lasting as long as the unaltered irritant remains in the lung.

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BENIGN TUMORS OF THE BRONCHUS.

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THE following study of benign tumors of the bronchus is based on 17 cases, 14 of which we have observed clinically and bronchoscopically with biopsy. The remaining 3 belong to an earlier period and are derived from the clinical and autopsy records of Mt. Sinai Hospital. We have included 2 cases of inflammatory polyp and 1 case of bronchial lymphoma. This has been done intentionally and may be justified in a study which is essentially clinical because these cases present the same problems in diagnosis and treatment as benign neoplasms and they have a similar pathogenesis.

These tumors, of which not more than 30 have been recorded.^{1*} possess a practical importance which outweighs their rarity. Chevalier Jackson² states that primary growths of the tracheo-bronchial tree though not frequent are by no means rare. Although they are characterized as benign, this is true only in a pathologic sense. If they are not discovered and removed they produce pulmonary complications which result in the death of the patient as surely as if they were truly malignant. Furthermore, we have

* The reader is referred to this article for a brief survey of the literature.



FIG. 1.—Benign tumor of the bronchus. Low power.

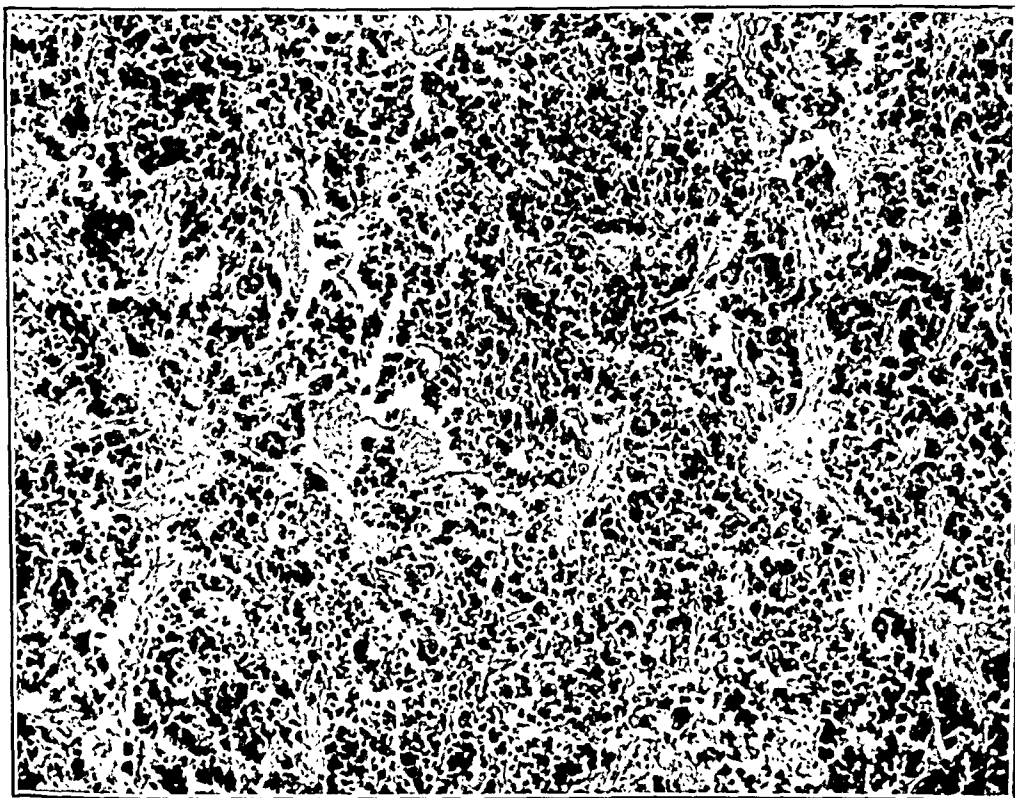


FIG. 2.—Benign tumor of the bronchus. High power, showing characteristic cellular structure.



FIG. 3.—Cross section of bronchus. Moderately enlarged, showing entire polyp. Note the extension of the adenoma between and behind the cartilages.



FIG. 4.—Adenomatous polyp in left main bronchus. Showing characteristic position; dilatation and infection of the distal bronchus and lung.

definite evidence which will be later adduced, that a benign bronchial tumor may years later undergo malignant degeneration. On the other hand if they are early recognized they are very amenable to treatment. For these reasons we present a pathologic study and clinical analysis of our cases and have attempted to formulate the data upon which a diagnosis may be made clinically. That this can be done with some measure of success is indicated by the fact that of the 14 cases which we personally studied a presumptive diagnosis was correctly made in 9 cases on purely clinical grounds.

PATHOLOGY. We preface the clinical features of benign tumors of the bronchi with an outline of the essential pathologic facts. Our observations are limited to the form of tumor known as the adenomatous polyp, as this is the commonest type of bronchial tumor and comprises 12 of our cases. Other types of tumors are occasionally found. Jackson² describes primary papillomata and fibromata. He also points out the tendency toward malignancy which is evidenced by some chondromata and osteochondromata.

Adenomatous polypi always originate from the mucous membrane of a large or main bronchus. The growth is commonly situated not far from the origin of the bronchus. It is usually pedunculated and is so placed that its free bulbous end is directed toward the trachea. This position is a consequence of its extrusion from its bronchus in the act of coughing.

The body of the tumor is usually oval, its shape being determined by the length of its pedicle and the caliber of the bronchus to which it adapts itself and which it completely fills. If the pedicle is long the tumor may be movable and thus, acting as a ball valve, produce obstruction either of the trachea or of a bronchus other than that from which it takes its origin.

MICROSCOPIC PATHOLOGY. The body of the tumor has a smooth surface and is covered by a layer of epithelium. This often shows a squamous metaplasia which may result in a hornified stratified covering. In the basal part of the tumor where it is attached to the bronchial wall, the epithelium may be normal or it may be made up of a stratified layer of columnar epithelium. Beneath this there is a completely intact basement membrane. Subjacent to the latter there is often a layer of loose connective tissue within which are numerous dilated bloodvessels. Erosion of these vessels often gives rise to bronchial hemorrhage.

The tumor itself is made up of rather small cells whose cytoplasm varies in size in different cases. The nuclei are usually small and either perfectly round or ovoid. Their striking characteristic is a uniformity and homogeneity of structure and staining qualities. They are usually arranged in acini with perfectly definite basement membranes. There are instances, however, in which the acinar structure is not present and the cells appear to form solid masses. In the process of fixation and embedding there is a tendency for

the cells to retract from the basement membrane which is perhaps more marked than is the case in most adenomatous tumors. (Figs. 1 and 2.)

This description of the minute pathology of benign adenomas accords in its essential features with that of a small number of similar cases which have been recorded in the literature as carcinomas. It is our belief, based on the clinical and pathologic study of our patients and a comparison with those reported, that a number of these reported cases were mistakenly considered carcinomas and that they were truly benign adenomas. In their microscopic reports the authors frequently pointed out that there was an infiltration of the submucosa between the cartilaginous rings which sometimes extended even behind the cartilages. This was regarded by them as evidence of malignancy. However, when one studies the anatomic position of the bronchial glands, it will be found that they are normally found not only on the internal aspect of the cartilages, but also between and externally to them. The presence of neoplastic tissue in these locations therefore does not signify malignant infiltration of the bronchial wall but results from the hyperplasia of normally situated glandular structures. (Fig. 3.)

In 2 of our cases which were studied postmortem, there was some evidence of infiltration of the deeper tissues of the polyp. This consisted of a few groups of cells which apparently lay in a stroma outside the glandular acini. In these cases the distinction between a benign and a malignant neoplasm becomes more difficult. On purely pathologic grounds, they would have to be regarded as carcinomas. On the other hand, both cases presented a long history of pulmonary disease and there was a total lack of any gross infiltration of the bronchi or the lungs which should have been present if they had been malignant. For these reasons the microscopic interpretation of material removed through the bronchoscope or even at autopsy must be made with considerable reservation and with due regard to the clinical findings. It is of course possible in the occasional case which shows this beginning infiltration of the stroma that the adenoma is in the process of transition to carcinoma. Such a coincidence is certainly conceivable and we have 2 cases which are fully described at the end of this paper in which this sequence of events probably took place.

The point of origin of benign adenomas has been in dispute. There are 3 structures in the bronchus from which they could arise namely, the bronchial epithelium, the mucous glands or the duct epithelium of these glands. The bronchial epithelium can be definitely excluded as the origin of the tumors because the latter are invariably covered by this epithelium and by an intact basement membrane. The tumors probably do not begin in the mucous glands as their cellular elements bear no resemblance to those of the glands. We have in fact, observed the mucous glands to be dis-

tinct from the tumor with no apparent transition into it. This leaves the duct epithelium as the probable point of origin of the tumor. The tumor cells closely resemble those of the ducts of the mucous glands and in 1 of our cases there was distinct evidence of proliferation of the ducts. In parts of the tumor there were dilated ducts which had undergone squamous metaplasia so that some of the acini were composed of stratified squamous epithelium.

In addition to the adenomatous tumors which represent the large majority of our cases, there are recorded in the literature fibromas, fibrolipomas and enchondromas. Although pathologically distinct from adenomas they are similar to them in their mechanical effects and symptoms.

The cases which we herewith report are summarized in the following table:

TABLE 1.—SUMMARY OF 17 BENIGN TUMORS OF THE BRONCHUS.

Case No.	Age.	Sex.	Type of tumor.	Duration.
1	28	M	Fibroma	1 year
2	35	F	Adenoma	13 years
3	18	F	Adenoma	5 "
4	26	M	Adenoma	3 "
5	26	M	Inflammatory polyp	9 months
6	48	M	Fibrolipoma	1½ years
7	47	F	Adenoma	5 "
8	30	F	Adenoma	11 "
9	64	M	Adenoma	30 "
10	35	M	Inflammatory polyp	5 months
11	54	F	Adenoma	3 years
12	62	F	Adenoma	6 months
13	32	F	Lymphoma	1½ years
14	48	M	Adenoma	2 weeks (?)
15	35	M	Adenoma	(?)
16	32	M	Adenoma	7 years
17	35	F	Adenoma	2 "

The cases are almost equally divided between males and females.

TABLE 2.—AGE INCIDENCE.

Age.	No. of cases
10 to 20 years	1
21 to 30 "	3
31 to 40 "	7
41 to 50 "	3
51 to 60 "	1
61 to 70 "	2

It will be seen that two-thirds of the cases occur before the age of 40 years.

CLINICAL COURSE. The key to an understanding of the clinical course of this disease in its various forms is a knowledge of the mechanical effects of endobronchial tumors of this type. Such effects of course will be entirely absent while the tumor is still small. There is every reason to believe that a benign tumor, if its growth is slow, may exist for years within a bronchus without betraying

its presence by any symptoms, even cough. However, owing to its vascularity, at any time during its growth there are apt to be recurring hemorrhages from the bronchi unassociated with any other symptoms. Hemoptysis, which is most characteristic of benign tumors occurred in 12 of our cases and was usually frequently repeated. In a number of cases it occurred for periods of $1\frac{1}{2}$ to 5 years and in one instance it was frequently repeated for 30 years. In this stage of the disease which may be called its nonobstructive phase because there is no occlusion of the bronchus, pulmonary tuberculosis is usually suspected because of the hemoptysis.

The really serious symptoms, those which are apt to bring the patients under observation, are due to the continued growth of the tumor which ultimately causes an obstruction or occlusion of a large bronchus. The consequences of such an obstruction are various and they depend upon the advent of infection which is rarely long absent when a bronchus is occluded. It therefore happens that the majority of cases with benign tumor presented themselves with symptoms of bronchial and pulmonary infection which had lasted for months or years. The essential clinical facts in our cases are summarized in the individual histories at the end of this paper. From these histories the following facts may be derived:

1. The first symptom may be an attack of pneumonia with or without pleurisy (Cases 1, 2, 3, 4, 7). We may assume that this was preceded by an atelectasis of the lung due to stenosis of a bronchus upon which the pneumonia was engrafted. Usually this initial pneumonia subsided and was succeeded by a stage lasting several months to 6 years during which there were no symptoms at all or cough with blood expectoration.

2. In 3 cases the initial symptom was a dry pleurisy (Cases 13 and 5) or pleurisy with effusion (Case 6) which occurred respectively $1\frac{1}{2}$, 5 and 13 years before. This was followed by a period of several years during which there were no major symptoms. We must here assume that the bronchostenosis gave rise to a low-grade infection of the lung with an inflammation of the pleura. After a variable lapse of time these cases progress to present the changes of the advanced stage of the disease.

3. Purulent infection of the pleura occurred in 3 of our cases. It is a direct consequence of suppurative disease of the lungs and as such usually is a complication of the later stages of the disease. In our 3 cases the existence of an underlying bronchial tumor was not suspected in spite of a previous history of cough and expectoration. The patients sought treatment because of the acute condition of the pleura which required surgical treatment. The bronchial tumors were discovered only at autopsy. In 1 case (Case 14), the empyema appeared to be the first symptom of the tumor. Although the history of only 2 weeks' duration is open to doubt, the fact remains that a bronchostenosis with suppuration of the lung must

have been more or less latent for some time and that no major symptoms were produced until the pleura was infected. In another case (Case 5), an empyema which had been drained some time previously continued to discharge pus and failed to close up because of an unrecognized tumor of the bronchus.

4. The inevitable termination of all cases of bronchial tumors, whatever their initial symptoms, is suppurative bronchiectasis and suppurative or indurative pneumonitis which are always found if the obstruction is not relieved in time. Apparently, the atelectatic lung can resist serious infection for years. The usual history of these cases is that of recurring infection of the lung with periods of temporary improvement until finally lack of drainage leads to the complete picture of suppurative disease of the bronchi and lungs with constant cough and profuse expectoration often mixed with blood. It has long been noted that following even a relatively short period of obstruction by a benign neoplasm, the bronchi in the affected lobe show a marked degree of dilatation. Clubbing of the fingers at this stage of the disease is usually present. In isolated cases anaërobic infection is engrafted on the existing disease so that the clinical picture becomes one of lung gangrene and necrotic cavities originating from dilated bronchi are found in the lungs at autopsy (Case 13).

SPECIAL SYMPTOMS. *Age.* It will be noted that two-thirds of benign tumors of the bronchus occurred before the age of 40 years. In view of the similarity of this disease to malignant tumors of the bronchi and lungs, this fact becomes of some importance in differential diagnosis, as most cases of carcinoma occur after the age of 40.

Dyspnea. A unique form of dyspnea which may be very extreme due to change of posture of the patient is especially worthy of comment and may be regarded as pathognomonic of benign tumor of the bronchus. This occurred in Case 9. The patient observed that on changing to the recumbent position, his dyspnea became alarming. This is obviously due to the ball valve action of a pedunculated tumor which is displaced from its bronchus and obstructs the trachea.

Partial occlusion of a bronchus may also produce a whistling or sonorous sound during respiration, which may be more or less constant and to some degree localized over the affected lobe. In Case 17 this adventitious sound disappeared when complete occlusion of the bronchus occurred.

Hemoptysis. There is 1 symptom of benign tumor of the bronchus which is so outstanding that it deserves detailed consideration. In fact, it is the one symptom which is characteristic of this disease and is referable to the tumor itself, rather than to its pulmonary complications. This symptom is hemoptysis.

In the first place, recurring hemorrhage may be the only symptom for years before bronchial obstruction becomes manifest. Even

cough may be absent at this period of latency of the growth and it seems probable that the benign tumor may produce considerable narrowing of the bronchus without any cough resulting, providing infection of the lung has not yet taken place.

Hemoptysis occurred as a more or less prominent feature in 10 of our cases. It was commonly small in amount but in a number of the patients was profuse. One patient bled every month in such large amounts that she was almost exsanguinated and required a number of transfusions. In 2 patients the bleeding occurred only at the menstrual period. If careful inquiry were made it would probably be found that hemoptysis is the initial symptom in a considerable percentage of the cases.

There are certain features of the bleeding which distinguish it from hemorrhage due to other causes in the chest. The hemoptysis is very apt to occur suddenly without any warning and unassociated with other symptoms of pulmonary or bronchial disease. What is more striking is that the bleeding may cease just as abruptly without any subsequent period of streaking or staining of the sputum as is commonly the case when blood is derived from actual disease of the lungs.

One may explain this in the following way. Hemorrhage from benign tumors occurs in a main bronchus and the blood exudes from very small submucous vascular spaces. It is probable that bleeding of this character is slow and that the blood is expectorated before it can pass down into the smaller bronchi. This is further prevented by the presence of the occluding tumor below the point of bleeding. All of the blood is therefore promptly expectorated and little or none is aspirated into the smaller tubes. With a more brisk hemorrhage however, especially where there is not yet a bronchial occlusion, it is of course possible for the blood to be aspirated and to undergo the chemical changes which result in expectoration of dark blood for some days. It is therefore characteristic of bleeding from an occluding benign tumor that the hemorrhage is unexpected in its onset and, whether mild or severe, is apt to be equally sudden in its cessation and it is not succeeded by a period during which dark or otherwise altered blood is brought up. In this respect the bleeding differs from that seen in actual disease of the lungs or the hemorrhage from a malignant new growth or from varices in the bronchus.

In the stage of bronchial occlusion with pulmonary infection the expectorated blood may be either pure or mixed with mucus and pus.

ROENTGEN EXAMINATION. The roentgen examination plays an important though indirect rôle in the diagnosis of benign tumors of the bronchi. The tumor of course is itself invisible on the roentgen films. It is only when it is sufficiently large to cause an occlusion of a main bronchus that any changes can be observed on the roentgen film. At first this consists of an area of atelectasis in the lung.

This is usually lobar in distribution except in the occasional instances when the main bronchus is obstructed. Under these circumstances a whole lung will appear cloudy. The shadow of a collapsed lobe is fairly characteristic. If the collapse occurs in a lower lobe, especially on the left side, it may be associated with an elevation of the diaphragm which may obscure the shadow of the airless lobe.

When infection has supervened the roentgen appearance differs in nowise from that in cases of chronic pneumonitis with bronchial dilatation or lung abscess. In this late stage of the disease the affected side of the chest is collapsed, the lung or a part of it shows a dense infiltration and the heart and mediastinum are drawn over to the diseased side. Unless the clinical history is available the roentgen appearance affords no basis for a diagnosis of bronchial tumor and one is at a loss to distinguish between chronic inflammatory disease of the lung, malignant new growth, advanced unilateral tuberculosis and finally, benign tumor of the bronchus.

BRONCHOSCOPY. The definitive diagnosis of benign tumor of the bronchus rests with the bronchoscopic examination. Everything that has gone before may be suggestive or strongly presumptive but only the bronchoscopic demonstration of the tumor furnishes a certain diagnosis. Invariably the bronchoscope discloses a smooth globular or oval tumor which may be sessile or attached by a pedicle and may thus be freely movable. In our series of cases the tumors had the following situations:

	Cases.
Right upper bronchus	1
Right middle bronchus	2
Right lower bronchus	6
Right main bronchus	1
Left upper bronchus	1
Left lower bronchus	4
Left main bronchus	2

PATHOLOGIC CHANGES IN THE LUNGS. The severity of the pathologic changes in the lungs bears a close relation to the duration of the bronchial occlusion. When, as in Case 11, the tumor caused no obstruction to the bronchus there were no changes in the lung. In the cases in which there was an occlusion of presumably short duration, simple atelectasis of a lobe was present associated with retention of bronchial secretion. This was found in 4 cases (Cases 2, 4, 5, 10). In those patients in whom the disease had existed for longer periods, bronchiectasis and infection and induration of the lung with their pleural complications had occurred.

DURATION. The exact duration of this disease is difficult to estimate because of the uncertainty of the time of its onset. The period of latency is variable and may be relatively long, as is evidenced by the patients in whom there were repeated hemoptyses for years. If bronchial bleeding or symptoms of pulmonary infection

are taken as presumptive evidence of a benign tumor we must conclude that the duration of the disease varies from months to years. The shortest history was 5 months and the longest 30 years. In the majority of cases symptoms pointing to the existence of a tumor were present for several years.

DIAGNOSIS. *Clinical.* The diagnosis of benign tumor of the bronchus presents 2 problems, first the recognition of this condition in the stage before bronchial obstruction, and second, in the stage of bronchial occlusion.

The Unobstructive Stage. Diagnosis at this time is more important as permanent damage to the lung has not yet occurred and removal of the tumor may result in a complete cure. However, the diagnosis is more difficult because the physical and roentgen examinations are negative. A tumor should be suspected when there are recurring bleedings from the bronchus which have the characteristics previously described. Such bleeding should at once invite bronchoscopy.

The Obstructive Stage. The diagnosis is of practical importance because the removal of the tumor may prevent the infection of a lung which is already collapsed; it may also cure a suppurative bronchitis and may even cause a pneumonitis to subside. However, in the longstanding cases when bronchial dilatation has occurred or actual suppuration of the lung is present, removal of the tumor will not lead to permanent improvement. The diagnosis rests upon a suggestive history of recurrent bleeding supported by the physical findings of obstruction of a bronchus and evidence of suppurative disease of the bronchi and the lungs. These latter findings are usually demonstrated by the roentgen film. Here again, the bronchoscope brings the only certain proof of the existence of a benign tumor.

Microscopic. We have already described the microscopic characteristics of adenomatous polypi of the bronchus. It is however, worthwhile to emphasize the errors in diagnosis which are likely to occur in the interpretation of the minute pathology of material removed through the bronchoscope. It has happened in several of our cases that tissue removed has been regarded by the pathologist who did not know the clinical features of the case, as carcinomatous. In Cases 4 and 16, for example, the microscopic report was carcinoma and endothelioma, although the condition had existed for 4 and 7 years respectively without any evidence of invasion of the lung. In Case 16 a diagnosis of endothelioma had been made 7 years before. Recently a recurrence of the symptoms afforded an opportunity for another microscopic examination which showed a typical adenomatous polyp. In such cases therefore, especially where the youth of the patient and the long duration of the symptoms indicate the probability of a benign tumor, the microscopic findings must be subjected to a critical appraisal.

PROGNOSIS. The prognosis of this disease follows from the preceding observations. It is closely related to the time when the diagnosis is made and depends entirely upon the removal of the tumor before permanent damage has been done to the bronchi and lungs. In 6 of our cases it was possible to remove the tumor and more or less completely relieve the patients of their symptoms, which have not recurred. In 1 case the tumor was removed after 4 years. There has been a tendency for the persistence of atelectasis of lobes which have been collapsed for some time. This apparently is tolerated with few or no symptoms providing the bronchus is patent. In 4 cases owing to the long duration of the disease with consequent permanent damage to the lungs there has been a persistence of the symptoms in spite of partial or complete removal of the tumor through the bronchoscope. In 1 case (Case 11), the diagnosis was made in the pre-obstructive stage because of bleeding. This tumor was so recently removed that nothing can yet be said of the final outcome. Two patients (Cases 7 and 13), died as the result of an empyema which was secondary to advanced suppurative disease of the lung. The diagnosis of bronchial tumor was only made post-mortem. Two cases (Cases 15 and 14) died, 1 after an operation for lung abscess and the other of a putrid empyema. Both showed extensive bronchopulmonary disease. The last 2 cases (Cases 16 and 17), which have come under observation recently are still under treatment. Although the tumors are being removed, the final outcome is in doubt because of extensive changes which have occurred in the lower lobes due to occlusion of the bronchus. It is not improbable that if drainage through the bronchus can be established the patients may have a symptomatic cure.

TREATMENT. The treatment of benign tumor of the bronchus consists in the removal through the bronchoscope of the obstructing tumor. Details of this treatment are discussed by Kramer in a recent publication³ to which the reader is referred. The complete removal of the tumor at once may not be possible. There is further a tendency in some cases for the growth to recur after an interval of years. In Case 16 this interval was 4 years, during which the patient remained in perfect health. The pulmonary complications of this disease may require surgical treatment such as the drainage of empyemas or suppurative foci in the lung. It should be especially noted that in cases of empyema of obscure origin, the possibility of an obstructing tumor of the bronchus should always be considered when there is persistent discharge of a sinus.

We append a short history of our 17 cases:

CASE 1.—S. S., aged 28 years. Male. September, 1920.

History. "Grippe" 1 year ago. Pneumonia with left pleurisy 8 months ago. Since then constant cough with expectoration and dyspnea on exertion. Eight weeks ago a recurrence of left pneumonia; for 3 weeks daily chills and fever.

Examination. Left chest smaller; left lung posteriorly dullness with absent breathing over lower lobe. Clubbing of the fingers. Chest aspirative negative. Temperature continued daily up to 104° F. until November, when bronchoscopy was performed. Two centimeters from bifurcation the lumen of the left bronchus was closed by a smooth, round mass covered by normal mucosa. It was attached to the outer wall above the opening of the upper branch and filled the lumen of the main bronchus almost completely. Pus issued from behind the tumor. After removal of the tumor the patient made a complete recovery, so that by December 22 all shadows had disappeared from the Roentgen film. The latter had previously shown a dense shadow of inflamed, collapsed lung with displacement of the mediastinum to the left.

CASE 2.—A. De G., aged 36 years. Female. February, 1929.

History. Right-sided pleurisy with effusion 13 years ago. Was ill for 3 months with fever. Nine years ago had "grippe" which was repeated three times since. One year ago there was a gush of 3 ounces of bright red blood from the mouth. This was at the time of her menstrual period. Since then she had two similar attacks, also at her menstrual period. Bleeding began and stopped abruptly. During this time the patient had frequent colds with pains in her right chest on breathing.

Examination. Signs of an infiltration over the right middle lobe with atelectasis. Thickening of the pleura at the right base.

Bronchoscopy: Showed a round mass covered with mucous membrane in the right middle bronchus, entirely occluding it. Specimen removed showed microscopically adenoma. After complete removal of the tumor patient remained well.

CASE 3.—N. MacQ., aged 17 years. Female. December 25, 1925.

History. During the previous 5 years she had frequent hemoptyses (perhaps 100) of 1 to 5 ounces of blood. These were at first more severe in the winter time when she had a severe cough. Since then they also occurred in the summer. They usually occurred at the menstrual period. Frequent nightsweats. Two months ago she had fever for 2 days and was told she had pneumonia. For 2 weeks patient felt warm in the afternoon. No loss of weight.

Examination. Patient well nourished and did not look ill. The whole right lower lobe was flat, with distant breath sounds and absent fremitus. Clubbing of fingers.

Bronchoscopy: Showed a tumor occluding the right lower bronchus, which bled easily. Microscopic examination showed an adenoma. Tumor could not be removed because manipulation caused alarming hemorrhage.

Patient was observed for 3 months, during which she had profuse large hemorrhages and periods of high fever. The signs in the lung were due to atelectasis and infection. Patient was not improved.

CASE 4.—J. P., aged 26 years. Male. August, 1926.

History. Began 3 years ago with pneumonia and pleurisy with effusion on left side. Then developed a cough with hardly any sputum. Two years ago he went to Colorado as a tuberculosis suspect because of hemoptyses. During the last 2 years he has had several fairly large hemoptyses. In Colorado he was declared nontuberculous. For the last 8 months cough was more persistent with dyspnea on exertion. No fever.

Examination. Signs of complete closure of the left lower bronchus. A loud rhoncus over the left lung. Roentgen examination showed collapse of left lower lobe with an elevation of the left diaphragm.

Bronchoscopy: Showed an adenomatous tumor at the origin of the left lower bronchus which completely filled it.

Subsequent Course. Patient was so much improved by bronchoscopy that he refused further treatment to remove the tumor. He remained

well until 1927, when he had a recurrence of his bleeding. In February he had an acute pneumonia with high fever, which subsided promptly after the removal of some tumor tissues through the bronchoscope. On March 23 three radium seeds were inserted in the bronchial wall at the site of the tumor.

Since then the patient has been free of cough or any other symptoms. Roentgen examination still shows some collapse of the left lower lobe, which is, however, gradually expanding.

CASE 5.—M. D., aged 38 years. Male. January, 1929.

History. Pneumonia 9 months before, with high fever and right pleural pain. This was followed by cough and blood-stained sputum for several weeks. Since then constant pain in the right chest anteriorly. Cough with no expectoration. Roentgen examination showed a shadow in right middle lobe due to atelectasis. Lung abscess had been diagnosed and a phrenicotomy performed.

Bronchoscopy: January, 1929. Showed middle lobe bronchus occluded by a gray lobulated tumor, 5 by 9 by 12 mm. This was removed with forceps. Microscopic examination showed an inflammatory polyp.

Subsequent Course. For some time the patient had a persistence of his pain. Repeated bronchoscopy for the removal of small recurrent polypoid masses. He is now well.

CASE 6.—J. F., aged 48 years. Male. March, 1929.

History. In 1917 the patient had "grippe" and pneumonia and was sick in bed 19 weeks. For 3 to 4 years he had slight burning pain in left upper chest. One and a half years ago he began to cough and continued to cough with greater frequency and increasing expectoration. This continued for 6 months, with increasing cough and so much dyspnea that he was told he had asthma. This became so severe that he could not lie down at night. One year ago the patient began to spit blood for 2 or 3 days at a time. This would begin abruptly. This continued to the present time.

Examination. Showed an infiltration in the mesial part of the left lower lobe. Marked clubbing of the fingers.

Bronchoscopy: Examination showed a pedunculated tumor in the left lower lobe. Following the removal of this tumor the patient made a rapid recovery.

CASE 7.—B. W., aged 47 years. Female. June, 1927.

History. The patient had pleurisy 5 years before admission and empyema 2 years later, for which thoracotomy was performed on the right side. A persistent sinus remained to the present time. Cough which had been present for at least 3 years continued with moderate amount of blood-streaked sputum. A diagnosis of lung abscess was made, for which a collapse operation had been performed in April. In June the sinus was injected to determine a communication with the bronchus which could not be demonstrated. In July, in an attempt to split open the sinus for better drainage, the patient bled to death through the fistula. Among other clinical findings the blood and urine showed signs of a nephrosis, resulting from the long-continued suppuration.

Autopsy. In the left lower lobe bronchus there was found a freely movable cylindrical pedunculated tumor, 21 by 6 mm. The bronchus distally was markedly dilated and opened into a cavity leading into a sinus to the chest wall. There were numerous sacculated dilatations filled with blood. The hemorrhage had come from a dilated branch of the pulmonary artery in the wall of one of the sacculations.

The tumor was composed of glandular structures, separated by thin connective tissue septa. It was an adenomatous polyp.

CASE 8.—J. K., aged 27 years. Female. September 20, 1929.

History. Eleven years ago the patient had influenza followed by pneumonia and pleurisy. Since then she had more or less constant cough. A few

times a year sputum was slightly bloody. She had many colds. One year ago she began to have slight dyspnea on exertion. Three months ago pain in the left chest with a great increase in the frequency of cough. Constant fever up to 101° and much loss of weight.

Examination. Chronically ill woman with a harrassing cough, with thick, blood-streaked sputum. Trachea displaced to the left. The volume of the left chest smaller than the right and moved less in respiration. Dullness in the upper part of the left lung increasing to flatness at the base. The breathing sounds in the upper lobe distant and absent at the base. Heart displaced to the left side. Slight clubbing of the fingers. Daily temperature from 101° to 102° .

Bronchoscopy: Trachea displaced to the left side. Complete obstruction of the main bronchus by a globular tumor mass, which bled profusely. This mass was situated 2 cc. from the bifurcation.

Microscopic examination: Adenoma. Patient refused further treatment and remains unimproved.

CASE 9.—I. L., aged 64 years. Male. September, 1926.

History. Cough for 30 years, with hemoptysis 4 to 5 times a year for 30 years. Five years, shortness of breath and substernal oppression. For 3 months precordial pain radiating down the left arm. Weakness, loss of 36 pounds and increasing dyspnea. Pain less on walking, becoming worse on lying down.

Examination. The patient was poorly nourished. Profuse purulent expectoration. Lungs, dullness over the left upper lobe. Marked clubbing of the fingers.

Bronchoscopic examination: There was a flat tumor in the left main bronchus near the orifice of the upper lobe branch. This tumor was covered with normal mucous membrane and moved to and fro. It partly obstructed the left upper lobe bronchus.

Röntgen examination showed a fibrotic infiltration in the left upper lobe.

Tumor was not removed and patient was unimproved.

The interesting feature of this case was the unusual type of dyspnea on changing to the recumbent position, which was evidently due to the upward displacement of the pedunculated tumor causing an obstruction of the trachea.

CASE 10. D. M., aged 36 years. Male. February, 1930.

History. Five months before admission the patient had a cough and coryza. Cough gradually became productive of small amounts of whitish sputum. On 6 occasions in the last 3 or 4 months he spat up 2 to 3 drams of blood preceded by a peculiar sensation under the sternum which disappeared after the blood was expectorated. Six months before admission he had his tonsils removed.

Examination. Well-nourished man. Signs of pneumonic infiltration over the right lower lobe, with a few râles and diminished breathing.

Bronchoscopy: Showed an irregular stenosis of the right lower lobe bronchus, which bled freely. Tissue removed was found to be an inflamed polyp. Patient was repeatedly bronchoscoped and bronchus dilated after removal of more polypoid tissue with gradual improvement of the symptoms. When last seen aëration of the right lower lobe had improved and, although bronchoscopy showed a cicatricial narrowing of the right lower lobe bronchus, patient was symptomatically well.

CASE 11.—I. B., aged 54 years. Female. October, 1930.

History. Twenty years ago the patient had a heavy cold with small hemoptysis. Sputum negative and not considered a case of tuberculosis. Three years ago she began to cough and coughed each winter, bringing up blood on 5 or 6 occasions. Amount of blood expectorated was $\frac{1}{4}$ cupful, lasting for 1 to 2 days, followed by streaking for 1 to 2 weeks. Three weeks before she had 2 hemoptyses.

Examination. Healthy looking woman with no signs of pulmonary disease. Roentgen examination of chest was normal.

Bronchoscopy: In posterior wall of left main bronchus just above lower lobe branch was a soft, small mass, which bled easily.

Microscopic examination: Although the gross appearance and the clinical history indicate definitely that this is a benign tumor, the microscopic examination shows some infiltration of the stroma which the pathologist would regard as suspicious of malignancy. This is one of the cases in which the pathologic data must be accepted with much reservation and the clinical facts should take precedence in the diagnosis.

CASE 12.—K. M., aged 44 years. Female. May, 1922.

History. Began with upper respiratory infection 6 months before with productive cough which became more and more severe. Sputum was gray and contained no blood.

Examination. Well-nourished woman. Constant dry cough. Lungs showed dullness with diminished voice and breath sounds over the right lower lobe. Marked clubbing of the fingers.

Roentgen examination showed a dense pneumonic infiltration of the right lower lobe.

Bronchoscopy: Three centimeters below the bifurcation the right bronchus was completely closed by a tumor. The tumor was covered with granular mucous membrane and had a benign appearance.

Microscopic examination: Showed adenoma.

CASE 13. D. L., aged 32 years. Female. October, 1919.

History. One and a half years ago pleurisy on the right side. Since then apparently well. Two weeks before she began to cough and brought up small amounts of purulent sputum. Following this, temperature arose to 102° F. She had some dyspnea.

Examination. Well-nourished woman. Acutely ill with dyspnea and cyanosis. Signs of an effusion in the right chest associated with pneumonia.

Roentgen examination showed a consolidation of the lung with multiple cavities and pleural effusion.

Thoracotomy performed for empyema and large amount of pus evacuated. Before she died, two days later, she expectorated foul purulent sputum.

Autopsy. There was an abscess cavity in the right lower lobe. In the wall of the right main bronchus projecting into the lumen there was a mass the size of a cherry, which almost completely occluded it. The bronchi distal to the mass were dilated.

Microscopic examination: Showed the tumor to be a lymphoma.

CASE 14.—C. S., aged 48 years. Male. April, 1913.

History. Onset 2 weeks before with cough, fever and pain in left lower chest. Little sputum.

Examination. Patient acutely ill with temperature 103° F. Dyspnea and severe cough. Signs of a pyopneumothorax on the left side. Patient died suddenly after operation.

Autopsy. Showed in the left lower lobe bronchus a cauliflower tumor, 2 cm. in diameter. The tumor was firm, not ulcerated and extended into the bronchial wall at its base for about 3 mm. No invasion of the peribronchial tissue.

Microscopic examination: Showed the tumor to be an adenoma.

Apparently the bronchial stenosis had resulted in pulmonary infection, with a secondary anaërobic infection of the pleura.

Comment. Although the duration of the symptoms is given as 2 weeks, this must be doubted.

CASE 15.—J. M., aged 35 years. Male. January, 1915.

History. A detailed history was not obtained. It was known, however, that the patient had been coughing and bringing up large amounts of

purulent sputum every day, as much as 5 ounces. This had occurred for a considerable time. A diagnosis of lung abscess was made and patient operated upon. He died suddenly during aspiration of the lung.

Autopsy. Showed a chronic pneumonitis of the right lung with universal extreme dilatation of all the bronchi. There was an abscess in the pleura between the middle and lower lobe which communicated with the middle lobe bronchus. In the right lower lobe bronchus there was a tumor, 2.5 cm. in diameter, situated 4 cm. from its origin. The tumor was smooth and firm.

Microscopic examination: Showed adenoma.

CASE 16.—J. L., aged 32 years. Male. December, 1929.

History. Onset 7 years before, with attack of "grippe" with fever and dry cough. Continued to have fever for 1 year with dry cough. In May, 1925, he was bronchoscoped and a tumor found in right lower bronchus. The tumor was microscopically diagnosed as endothelioma. During the next year he had hemoptyses every 4 months of 1 to 2 cupfuls of bright red blood. He was then given a course of 12 treatments with the Roentgen ray over the tumor. Following this for nearly 4 years he remained well without cough or expectoration.

Two nights before admission to the hospital he brought up several tablespoonfuls of bright red blood. Bleeding became more active and on admission he brought up 1½ cupfuls of bright red blood with clots.

Examination. Patient was well nourished. Bleeding actively from his bronchus. Lungs: Dullness, diminished breathing, voice and breath sounds in the right lower lobe. No clubbing of the fingers.

Bronchoscopy: Showed a mass growing from the spur of the right main bronchus, blocking the right lower lobe branch. The mass was smooth and covered with a vascular mucous membrane.

Microscopic report: Adenoma. It is obvious that the previous diagnosis of malignant growth of the bronchus was incorrect. The adenoma is now being removed by electrocautery through the bronchoscope. The right lower lobe is collapsed and probably indurated.

CASE 17.—H. F., aged 35 years. Female. January, 1931.

History. Two years ago the patient had a sensation of pressure over the right lower chest anteriorly. From then until 4 months ago she felt in good health, but was aware, more or less constantly, of a whistling noise in her chest which she attributed to asthma, although she had no shortness of breath. Four months ago she got a sudden pain in her right chest, with fever and a dry cough. These symptoms have continued to the present time, with the addition of a small hemoptysis recently. She had no expectoration.

Examination. Well-nourished woman. Daily temperature up to 101° F. Marked clubbing of the fingers. Lungs: Dullness over the right lower lobe with much diminished breathing. A loud rhoncus is heard over the entire right chest which is more or less constant.

Roentgen examination: Showed an infiltration of the right lower lobe with numerous bronchial dilatations of large size.

Bronchoscopy: Showed a tumor completely occluding the right lower bronchus which on microscopic examination proved to be an adenoma.

The history of this case indicates that there was a tumor in the right lower lobe bronchus for at least 2 years, with probably atelectasis of the right lower lobe. The active symptoms of the disease began 4 months before with an infection of the lung which has since continued.

We wish in conclusion to record some observations which appear to indicate that a benign tumor of the bronchus may undergo a

transformation into a carcinoma with invasion of the lung. In the following 2 cases, the clinical course of the disease and the pathologic findings indicate that this was probably the sequence of events.

CASE 18.—E. F., aged 33 years. Female.

The clinical symptoms began in April, 1921, with cough and expectoration of a small amount of blood. After 4 months of quiescence the same symptoms recurred, together with some fever and dyspnea. Patient was then well for 6 months, when her cough returned. When first examined, in April, 1922, she had lost 33 pounds. She presented on physical examination an atelectasis of the left upper lobe. The bronchoscopic examination showed a compression of the left lower lobe from which creamy pus issued, but no tumor was seen. The patient lived until the early part of 1929 with symptoms of suppuration of the lungs, when she finally died. At autopsy, a polypoid tumor was found obstructing the left main bronchus, with a secondary suppurative disease of the left lung with multiple cavities. Microscopic examination showed carcinoma.

We have here a case which lasted for 8 years and showed at autopsy a malignant tumor of the bronchus. It is not likely that a carcinoma of the lung could have existed all this time. The polypoid appearance of the tumor (Fig. 4) and the long history of proven stenosis of the bronchus with pulmonary infection can lead to no other conclusion than that originally and for a number of years thereafter the tumor was a benign adenoma, and only latterly did it undergo a malignant degeneration at its base.

The next case, though of shorter duration warrants the same conclusion in regard to the pathogenesis of the tumor.

CASE 19.—H. S., aged 33 years. Male. February, 1928.

History. Patient had cough every winter for a number of years, with occasional spitting of blood. Two months previously he caught cold with an increase of his cough and some fever. He had pain in his right chest for 3 weeks with spitting of bloody sputum.

Examination: The patient was acutely ill with fever. Physical examination showed a pleural effusion occupying the lower two-thirds of the right chest. There was some clubbing of the fingers.

Bronchoscopic examination: Showed a bilobed round mass in the right main bronchus near the upper lobe branch covered with normal mucous membrane and dilated vessels. In the lower part of the main bronchus there was an irregular granular mass. This proved microscopically to be a carcinoma originating from the submucous glands. The patient later died of pulmonary hemorrhage.

In this case the history of cough with spitting of blood for a number of years makes it likely that the smooth polypoid tumor which was seen in the bronchus had probably been benign and had existed for some time and that only recently it became malignant. This is further borne out on the roentgen film by the absence of any infiltration of the tumor into the lung.

Our experience in these 2 cases, in which a carcinoma developed from a preëxisting benign polypoid growth, is an added reason for the prompt removal of these tumors.

Summary. Based on a study of 17 cases, we have sought to define a clinical picture of benign tumors of the bronchus. Our study has been concerned mainly with that form of tumor known as adenoma, which appears to be the commonest type encountered clinically. The following facts are emphasized.

1. Care must be exercised in the microscopic diagnosis of these tumors lest they be mistakenly regarded as malignant.

2. Benign tumors of the bronchus probably have a long period of latency during which there may be no symptoms of bronchial obstruction or bronchial irritation.

3. In a considerable percentage of the cases this period is characterized by repeated hemorrhages.

4. Aside from the symptoms of bronchial obstruction and infection, pulmonary hemorrhage is a frequent symptom of adenoma of the bronchus. This bleeding has certain characteristics which may suggest the diagnosis.

5. When stenosis of a bronchus with infection of a lung has occurred the clinical picture may be confusing. These clinical pictures are described.

6. The prognosis of benign tumors of the bronchus depends upon the early discovery and removal of the tumor, which may lead to prompt cure. When secondary inflammatory changes have occurred in the lung, the outlook is not good.

7. Evidence is adduced which indicates that polypoid adenomas may undergo malignant degeneration.

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THE FREQUENT OCCURRENCE OF ABNORMAL CUTANEOUS CAPILLARIES IN CONSTITUTIONAL NEURASTHENIC STATES.

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In 1912 Lombard described a simple method for direct microscopic examination of the minute vessels of the human skin. He rendered the superficial epithelium transparent by applying gly-



FIG. 1.—Normal capillaries in a man aged 40 years. The hairpin form predominates.

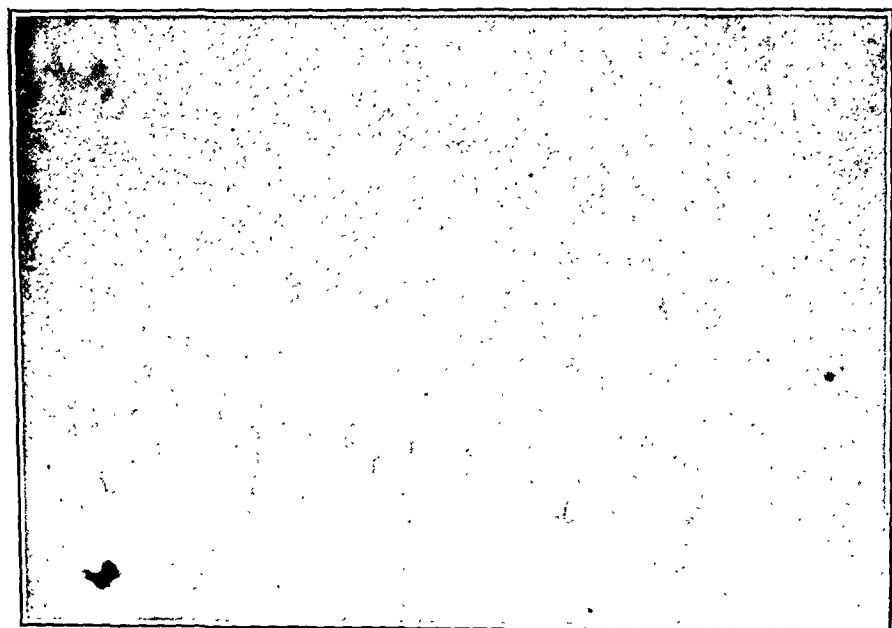


FIG. 2.—Capillaries in a man, aged 65 years, with marked arteriosclerosis. Cork-screw forms are frequent. The subpapillary venous plexus shows with unusual distinctness.



FIG. 3.—Capillaries of Case 1, showing abnormally shaped forms. Note the intricate pattern of the central capillaries.

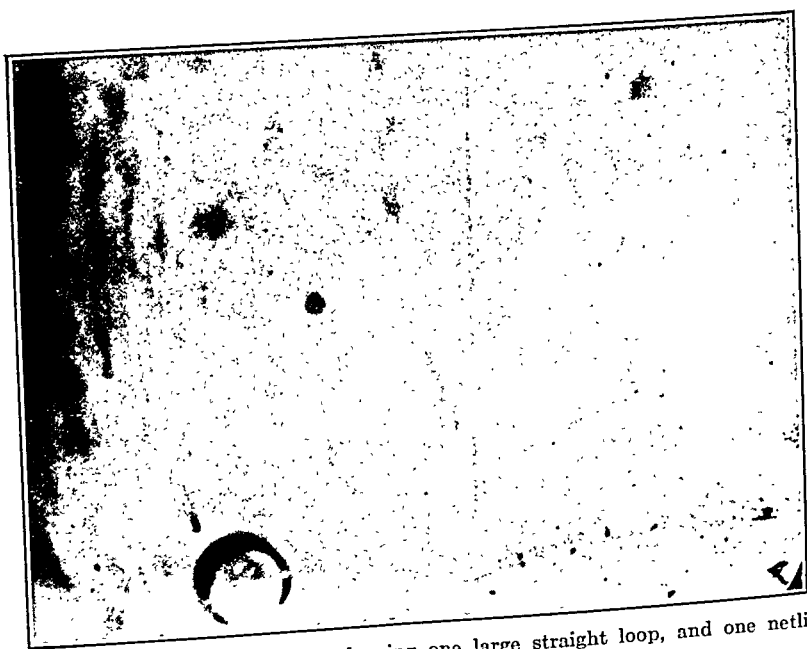


FIG. 4.—Capillaries of Case 2, showing one large straight loop, and one netlike formation.

cerin or cedar oil, and inspected the skin directly through the microscope, using a strong, oblique light. The skin just back of the nail was found most suitable for observation, for there the capillaries course more nearly parallel with the skin surface, and are, therefore, visible through most of their extent. Ordinarily they are hairpin shaped, of fairly uniform size and arranged in parallel rows, connecting the subpapillary venous and arterial plexuses. The subpapillary venous plexus is superficial to the arterial, and is frequently visible. Brown⁵ gives the average visible length of the capillary loop as 0.42 mm., with a width of 0.007 mm. for the arterial and 0.009 mm. for the venous limb. Frequently loops are rotated, constituting the corkscrew forms. Since Lombard's work many reports have been published describing capillary changes considered characteristic of many diverse conditions, including Raynaud's disease, acrocyanosis, scleroderma, erythromelalgia, arteriosclerosis, nephritis, primary and severe secondary anemias, purpura, diabetes, polycythemia, certain neurasthenic states, and certain cases of idiocy.

The engorgement and widening of the vessels in polycythemia vera was well shown by Brown and Giffin.^{3,6} The converse, the thinning of the caliber in severe anemias, is also generally accepted. Probably the most exhaustive capillary studies were those made by Ottfried Muller with his associates, E. Weiss, Niekau, and Parrisius. He describes dilated fantastically coursing capillary forms with an intermittent type of bloodflow in Raynaud's disease, erythromelalgia, acrocyanosis, and in certain neurasthenic states that he terms the "vasoneurotic diathesis." In acrocyanosis the intermittency of flow is least marked, and there is definite capillary dilatation, especially on the venous side. Brown⁵ in studying a series of cases of Raynaud's disease, described periods of interference with capillary bloodflow during typical attacks, believed due to spasm in the arterial system. Brown and O'Leary⁴ report two capillary pictures in scleroderma; the one identical with Raynaud's disease and followed they believe by secondary scleroderma; the other with huge dilated atonic capillary loops, even large enough to be visible macroscopically at times, associated with primary scleroderma. In diabetes, Muller and his associates have described a thickening of the midportion of the capillary loop, at the junction of the arterial and venous limbs, but this is denied by most observers. The German investigators have seen minute capillary hemorrhages visible only microscopically in purpura. Powdermaker, reviewing the work of Hoepfner, Jaensch, Wittneben, Weygandt and Kahle, and adding some observations of her own, describes an abnormal capillary picture in congenital idiots, especially common in those with associated physical maldevelopment, which she believes to be due to persistence of fetal and infantile forms. In nephritis, E. Weiss says the number of capillary loops is increased, and the individual vessels

are longer and wider than usual, and are greatly looped. This finding has not been confirmed by others.

Under the term "vasoneurotic diathesis" Muller describes a syndrome with a clinical and a capillary part. Patients with this condition may have any of the symptoms or symptom complexes which ordinarily lead to the diagnosis of neurasthenia or psychasthenia. They are persons who have belonged to this category since early childhood, and are totally unable to cope with an even moderately exacting environment. Emotionalism and a subjective and objective vasomotor instability are prominent symptoms. They are said to weep and blush easily, and their hands are cold and clammy most of the time, especially under stress. Their capillaries are disordered in arrangement, variable in size, but, most pathognomonic of all, show fantastically coursing and frequently large forms. The intermittency of the flow is not so marked as in Raynaud's disease, and the widening of the diameter is not so great as in Raynaud's disease, erythromelalgia, or acrocyanosis. However, the differential diagnosis from the organic vascular disturbances just mentioned can best be made by the clinical history. L. A. Miller^s mentions the condition and states that he has seen 3 such cases which he does not report in detail.

In this investigation some 600 cases were studied, including patients in the wards and the outpatient departments of the University Hospital. These patients presented a great variety of clinical conditions. For the purpose of this paper, patients with obvious peripheral vascular disease or engorgement, including acrocyanosis, Raynaud's disease, polycythemia and scleroderma are excluded.

Over 500 cases were studied that showed no evidence of organic peripheral vascular lesions, other than perhaps a sclerosis commensurate with age. In 31 of these cases the diagnosis included a functional "neurasthenic" condition. Of these 500 cases, 8 cases showed a definite morphologically abnormal capillary picture. By that is meant that a considerable number of the capillaries viewed in practically any field are abnormal. The clinical diagnoses were interesting. Two were diagnosed simply as psychoneurosis; 1 as psychasthenia; 2 as neurocirculatory asthenia; 1 as neurasthenia and hyperthyroidism (?), the (?) because the basal metabolism was normal though there was a slight goiter; 1 as vasomotor neurosis and essential hypertension; and 1 as infectious arthritis and infected tonsils. This last case (No. 1 in the case histories) alone did not have a functional diagnosis, even in part, though from the records it is fairly obvious that one could easily have been made. It will thus be seen that all 8 cases are included in the 31 with a functional diagnosis in whole or in part. These cases, as will be shown later, fall fairly well into the clinical syndrome described by Muller. However, it is also to be noted that 23 cases with similar diagnoses had perfectly normal capillary pictures.

Method. The light from a 500-watt lamp is cooled by passing through a spherical liter flask of water and concentrated by a single planoconvex lens to fall upon the stage of an ordinary microscope at an angle of about 45° . A 7.5 ocular and a 32 objective were found most suitable for observation and for photography. For observation the unprepared skin of the finger just back of the nail was covered with cedar oil and examined on the stage of the microscope supported only by the grasp of the examiner. For photography the finger was placed in a small wooden box gently but firmly supported with plasticine, the arm resting on pillows, and the box strapped with adhesive to the stage of the microscope. In addition, a fragment of a cover glass was usually placed on the cedar oil to prevent bubbles in the field. The capillary circulation in the area to be photographed was observed before and after this manipulation, and in no case reported did any obvious change occur. Though an attempt was made to choose a representative field, it was usually necessary to select the area opposite the middle of the nail which is in general the flattest area and where the greatest number of loops appear in a single focus. For technical reasons, considering the support of the hand on the stage, the ring finger was found to be the most convenient. Photographs were made using a Leitz camera, style Maccam, taking Wratten and Wainwright panchromatic plates, size $3\frac{1}{4}$ by $4\frac{1}{4}$ inches. An exposure of one second was required.

In the following case reports, all fingers of both hands were examined and the ring finger of the left hand photographed. All photographs are untouched. Magnification is $\times 32$, *i. e.*, 1 mm. on the finger equals 32 mm. on the plate. Although these photographs are far from being technically perfect, it should be noted that they are untouched and at least as good as others of their kind. They should not be compared with drawings of capillary loops or "touched up" photographs.

Material. Figs. 1 and 2 illustrate normal cases. The first is of a man aged 40 years. His loops are overwhelmingly of the hairpin type. The visibility is rather good, and more than the distal line of loops are clearly shown. Here and there a short section of the venous plexus is seen, but this is not nearly so obvious as in the second case, a sclerotic individual aged 65 years, in whom the broad streamer plexus is plainly visible at the base of the loops. This visibility or nonvisibility of the venous plexus is purely a matter of individual differences, but the increased tendency to corkscrew forms in the distal loops of the older man is usually considered typical of arteriosclerosis.

The first and second cases reported are illustrated in Figs. 3 and 4, while the last 6 cases are not illustrated.

Case Reports. CASE 1.—R. S., a young woman, aged 26 years, had been extremely nervous since childhood. Her hands would become icy

cold and tremble on the slightest provocation. This emotionalism had prevented her from getting along in school or from holding a position afterward. Eleven months before admission, during pregnancy, she first noticed some pain in both elbows, worse on motion. At times her fingers felt stiff. This condition continued in a rather mild form until admission. Physical examination was essentially negative, except for very slight limitation of motion in the joints above mentioned. Pulse rate was not elevated. Blood count, urinalysis, blood urea nitrogen, blood Wassermann, gynecologic consultation, cervical smear for gonococci, gonococcus complement fixation, chest Roentgen ray—all revealed nothing significant. Joint Roentgen ray showed a slight thinning of interarticular cartilages of both elbow joints, and possibly slight periarticular thickening about certain interphalangeal joints, but no bony change anywhere. Tonsils were found to be diseased and were removed. Clinical diagnosis was infectious arthritis and infected tonsils.

During her stay in the ward she would weep when her bed was approached on ward rounds. Finally in an emotional outburst she left the hospital against advice. Fig. 3 shows the capillaries of this patient. The variation from the normal hairpin and corkscrew forms is striking. The demarcation between the corium and the epithelium shows with unusual clearness.

CASE 2.—B. L., a woman, aged 35 years, came of what she described as a nervous family. From early childhood she had been emotionally unstable, subject to cold hands on the slightest provocation, and had been addicted to biting her nails. She had married and was leading a sheltered life in her home. Three years before admission she had begun to suffer with headaches and at times felt quite dizzy. It was found that she had high blood pressure. She was never incapacitated from her household duties which were, however, not heavy. During the 6 months in which she was followed in the ward and dispensary her systolic blood pressure remained at 200 or a little over, while the diastolic remained at 130 to 140. There was no definite sclerosis, except in the retina, where there was slight angiosclerosis reported. Blood count, urine, phenolsulphonephthalein kidney function test, blood urea nitrogen were all within normal limits. A diagnosis was made of essential hypertension and vasomotor neurosis. Her capillaries are pictured in Fig. 4. Note one large, fairly straight loop and a netlike formation beside it. The last formation, somewhat resembling a glomerulus, is difficult to photograph because its blood channels do not all lie in the same plane.

CASE 3.—J. D., a man, aged 29 years, had always been extremely nervous, emotional and subject to cold hands and feet under slight emotional stress. Three years prior to admission he became definitely worse, with epigastric distress, belching, occasional palpitation and heart consciousness, general nervousness and irritability. He said that when his boss called him into the office he felt as though something had been turned off inside him. Diagnoses prior to admission had been psychoneurosis, hyperthyroidism.

The blood pressure was 126 systolic and 88 diastolic. Hemoglobin was 98 per cent and the red blood cell count 5,400,000.

He was somewhat underweight, but otherwise his general physical examination was negative. Examinations of his urine, blood sugar, blood urea nitrogen, basal metabolic rate, blood Wassermann, gastric analysis, Roentgen rays of heart, lungs and gastrointestinal tract and electrocardiogram all revealed nothing abnormal. Pulse varied between 110 and 62, averaging about 80. A diagnosis of psychoneurosis was made. Capillary examination showed a picture very similar to Fig. 3, except that there were also a considerable number of large, straight loops, as seen in Fig. 4.

CASE 4.—M. M., a woman, aged 27 years, had never been in good health. She had been nervous, somewhat emotional, subject to cold hands and feet

under stress. However, she carried on fairly well until 3 years ago, when she noticed increasing nervousness, irritability, palpitation and loss of weight. She was diagnosed hyperthyroidism elsewhere without a basal metabolism test, and treated with Roentgen ray with transient benefit. Physical examination showed nervousness and slight thyroid enlargement. Basal metabolic rates, as outpatient, +10 and +22; in the hospital, +3. The pulse rate varied between 60 and 100, averaging about 80.

The blood pressure was 130 systolic and 90 diastolic. Hemoglobin was 75 per cent and red blood cell count, 4,200,000. A diagnosis of neurasthenia and hyperthyroidism (?) was made. Capillary examination showed a picture essentially similar to Fig. 3.

CASE 5.—F. W. S., a man, aged 27 years, had always been nervous. He would have palpitation on any emotional excitement, and his hands would get cold and tremble. This dated from childhood. In December, 1929, he developed a slight cough and seemed definitely worse. He was happy in his work, and had not been subjected to any additional emotional strain, except a sexual one. His wife had been pregnant twice. The first child lived only 4 days and a second child was stillborn. His wife had been told that a third pregnancy would seriously jeopardize her health. For the past year or two the patient had been living in dread that this might occur.

The blood pressure was 165 systolic and 105 diastolic. Hemoglobin was 102 per cent, and red blood cell count 5,300,000.

Physical examination showed a sclerosed left drum and a nasal septum deviated to the right. Examinations of the urine, basal metabolic rate, chest Roentgen ray, blood urea nitrogen, Wassermann and phenolphthalein test all revealed nothing abnormal. Sinus disease was found and sinus surgery begun. Pulse varied between 100 and 70 while in the ward, averaging close to the lower figure. A diagnosis of psychoneurosis was made. Essential hypertension was suggested but not definitely diagnosed, because of the systolic blood pressure of 165. Capillary examination showed a definitely abnormal picture very similar to Fig. 3.

CASE 6.—M. C., a woman, aged 33 years, had been sickly and emotional since childhood. Her hands and feet were almost constantly cold, especially under stress. Four years before the time of first examination she had been found to have diabetes and had been treated for it with diet and insulin, with excellent results. Her mental condition was markedly abnormal. She would at times have strong imperative impulses to cry out and make a scene. Again she would be weak with terror for fear two automobiles, though distant and going slowly, would collide. She was self-conscious in crowds, and imagined people were looking at and talking about her. She had worked at routine factory tasks at times, but left capriciously when she took a dislike to her position. She had no definite illusions or delusions, and her intelligence was fairly good. The psychiatric consultant made a diagnosis of psychasthenia.

Physical examination and blood count were essentially normal. There was no pulse elevation and no thyroid enlargement. Basal metabolism was not tested. Capillary examination showed a picture in all respects similar to Case 1, pictured in Fig. 3.

CASE 7.—M. O., a woman, aged 25 years, who had never been in good health, complained of "poor circulation" since childhood, manifested by cold hands and feet. She had always been nervous, and worried so much she thought it kept her thin. Since the age of 20 years she had had frequent colds, leaving her with a dry, unproductive cough most of the time. Moreover, she had almost constantly a feeling of soreness under the sternum.

Physical examination showed an alert, slender, prematurely gray woman; right kidney was palpable and tonsils were diseased. Otherwise physical

examination was negative. Blood count, urinalysis, blood Wassermann, chest Roentgen ray, sputum examinations, electrocardiogram and basal metabolism revealed nothing significant. The orthodiagram showed a heart 18 per cent below average size. A diagnosis of neurocirculatory asthenia and visceroptosis was made, and a pharyngitis suggested as cause of cough.

Capillary examination showed essentially the same picture as seen in Fig. 3.

CASE 8.—S. H., a woman, aged 28 years, had led a sheltered life and was apparently well until July, 1929, when she noticed increasing nervousness, tremor of the hands and nervous instability. She had lost some weight, and her hands and feet perspired a great deal, and at times felt numb and tingling, but never cold. The onset of symptoms followed by one year the birth of her only child. There was, however, no previous history of nervous strain.

Blood pressure was 110 systolic and 72 diastolic. Hemoglobin was 93 per cent and the red blood cell count 4,600,000. She had a slight tremor of the fingers, slightly enlarged thyroid and a tachycardia of 140 on admission. Examination was otherwise essentially negative. Examination of urine, blood sugar, blood urea nitrogen, basal metabolic rate, van den Bergh, electrocardiogram, blood Wassermann, chest Roentgen ray, fractional gastric analysis, all revealed nothing abnormal. While in the ward she wept over trivial circumstances, and her pulse fluctuated widely between 140 and 70. Her nervousness practically disappeared while in the ward. A diagnosis of neurocirculatory asthenia and simple goiter was made. Capillary examination showed a picture quite similar to Case 3.

Discussion. A functional "neurasthenic" quality appears to be the clinical common denominator found in these 8 patients. This has been present, except in Case 8, from early childhood. Peripheral vasomotor instability is a prominent symptom. It is true that one patient has an early arthritis, and another an essential hypertension, but many other patients examined with these conditions failed to show any morphologically abnormal capillary change. On the other hand, most of the patients diagnosed under one of the neurasthenia categories showed perfectly normal capillaries. In the present series, some 23 such patients were examined and found to be perfectly normal as concerns nail-bed microscopy. According to Muller, onset at an early age and the prominence of symptoms due to vasomotor instability are the two factors most suggestive of the syndrome he describes. The record of these 8 patients would somewhat support this. In the history of the other 23, with 2 exceptions, symptoms dated from an emotional or psychic shock and not from early childhood. Moreover, in this larger group, vasomotor symptoms were much less prominent. This difference could not have been due to leading questions, for in every case the same questions were asked and the history was elicited before capillary examination, and never amplified later.

Summary. 1. In the absence of any of the recognized peripheral vascular diseases, abnormal cutaneous capillary configurations as seen at the nail bed, are most apt to occur in conjunction with neurasthenic states.

2. In the present series of 31 cases of "neurasthenia" studied, 8 showed abnormal cutaneous capillary configurations. Of these 8, all but 1 dated their symptoms from early life. Of the remaining 23, only 2 had a similar early onset, the remaining 21 apparently being initiated later by a psychic or emotional shock.

3. Vasomotor symptoms were universally present to a marked extent in the 8 with abnormal capillaries, and either absent or present to a lesser extent in the remaining 23.

4. It would seem that abnormal configuration of nail-bed capillaries in the absence of any of the recognized peripheral vascular diseases, suggests a neurasthenic state dating from early life and a constitutional nervous instability.

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RAYNAUD'S DISEASE: A CRITICAL REVIEW OF MINIMAL REQUISITES FOR DIAGNOSIS.*

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THE concept of the disease or disturbance first fully described by Raynaud has varied from that held by those who deny the existence of such an entity, to that held by those who include under the term

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all vascular disturbances associated with intermittent changes in color of the skin, and all grades of gangrene. The increasing amount of literature attests to the tendency to utilize the terms "Raynaud's disease" or "Raynaud's syndrome" as a general depository for a heterogeneous group of cases far removed from the condition originally described by Raynaud. Frequently in the literature one sees the statement "a typical case of Raynaud's disease," yet close examination of the report shows no similarity of the case presented to one of Raynaud's disease. The problem then resolves itself into this: should the diagnosis be reserved for a carefully defined condition, with characteristics sufficiently common to all cases for the condition to be designated as a disease, or should its boundaries be so extended as to include the larger and more inclusive group of vasospastic disturbances?

This study, then, attempts to review and analyze the cases reported by Raynaud to ascertain his allegiance to his criteria, to review a group of cases from the literature for the same purpose, and then to attempt to decide whether Raynaud's concept of this condition should be left unchanged or should be subject to certain revisions.*

Criteria of Raynaud. *The Occurrence of Gangrene Without Arterial Occlusion.* "I propose to demonstrate . . . gangrene affecting the extremities which it is impossible to explain by arterial occlusion" (page 8).† "There are gangrenes without alteration of vessels" (page 9). ". . . The variety of gangrene which I shall discuss . . . the arteries remaining permeable" (page 17). "All (of these gangrenes) present as a common character, absence of material obstruction to the course of the blood" (page 31). "The pulse never ceases to be perceptible . . . but it may present remarkable alterations" (page 107). "There actually occur . . . spontaneous vascular spasms, inappreciable in the great vessels, but very obvious in the arteries of small caliber" (page 155). "In symmetrical gangrene the pulsations (of the peripheral arteries) sometimes irregular, are ordinarily normal" (page 113).

Symmetry of Gangrene. "A variety (of gangrene) characterized especially by a remarkable tendency to symmetry . . . always affects symmetrical parts, the two upper or lower limbs, or the four at the same time; further in certain cases the nose and ears" (page 8). "I have been struck with the remarkable tendency of the mortification to affect symmetrically similar extremities . . . symmetrical parts which become affected together in a very great majority of cases. . . . Some (cases) deviate from the type more or less . . . but the tendency to localize itself at the same time

* If similar critical analyses were carried out in various eponymic diseases, such confusion would be avoided, in our opinion. [EDITOR'S NOTE.]

† The pages apply to the edition of Raynaud's work to which reference is made in the bibliography.

to the right and left halves of the body . . . would suffice, I think, to justify the titles of symmetrical gangrene" (page 98).

The Occurrence of Local Syncope. "One or more fingers become pale and cold all at once; in many cases it is the same finger which is always first attacked; the others become dead successively and in the same order. The attack is indolent; the duration varies from a few minutes to many hours. The cutaneous sensibility becomes blunted, then annihilated; the fingers become like foreign bodies to the subjects . . . , their temperature is notably lowered" (page 99).

The Occurrence of Local Asphyxia. "In the more pronounced cases, those in which the asphyxial symptoms predominate, the pallor of the extremities is replaced by a cyanotic color . . . sometimes it is bluish white, sometimes it is violet or slate colored, even becoming black" (page 101).

The Occurrence of Localized Rubor. "Finally (following cyanosis) a patch of red is formed on the extremities of the fingers. This patch gives place to normal pink color, and then the skin is found to have entirely returned to the primitive conditions" (page 101).

Type and Occurrence of Gangrene. "Sometimes the digits become entirely black and insensible, small phlyctenulæ appear upon one digit, . . . then on another, always at the extremity The small excoriation which results from it (the phlyctenula) persists some days. To see this lividity, this glacial cold, one would believe that the gangrene was about to extend more and more; but the malady recedes, the parts become reanimated, the small ulcer cicatrizes and contracts and there results a kind of conical tubercle immediately subadjacent to the nail" (page 105). "In a general way one may say that the most profound gangrenes are those which go to the length of causing the fall of many ends of fingers or toes" (page 108). "Symmetrical gangrene is mostly limited to the skin or to a very small extent beyond as, *e. g.*, to the extremity of the unguis phalanx" (page 113).

"Finally . . . we see gangrenous points appear on the extremities . . . may occupy the superficial layers of the skin from the extent of a pin's head up to the end of a finger, rarely more" (page 153). "The termination even in this grave form . . . is for the most part favorable. The sloughs detach themselves . . . cicatrization takes place" (page 108).

Intermittency of Attacks of Color Changes. "But it is . . . important . . . that cyanosis . . . related . . . to an organic lesion . . . the cause being permanent, the effect is also . . . there are no intermissions, although this obtains in local asphyxia" (page 102). "The attack (of pallor) is indolent, the duration varies from a few minutes to many hours" (page 99). "The period of reaction (from cyanosis) is accompanied by tingling sensations. . . . Livid patches appear on the cyanosed

parts. . . . This patch gives place to normal pink color" (page 101).

Review of Raynaud's Cases. There is no equivocation in Raynaud's statements as to the absence of organic arterial occlusion in the disease described by him. This absence of organic arterial disease is the chief premise presented by him. His entire thesis hinged on it. He believed, however, that diminished pulsation in the peripheral arteries, when present, was evidence of spasm. This doubtless allowed him to include cases of organic occlusive arterial disease in his two theses, for it has been shown^{1,2,3} that organic disease of the digital arteries associated with vasomotor changes, may occur in the presence of normal or diminished pulsations in the usual palpable arteries; namely, radial, ulnar, dorsalis pedis, and posterior tibial.

It is interesting that in the presentation of 31 cases, in Raynaud's two theses, the state of pulsations in the peripheral arteries was not mentioned in 14 (45 per cent). If we hold to his chief premise of gangrene without arterial occlusion we must exclude Cases 1, 2, 4, 5, 7, 16, 17, 20, 21, 23, 24 and 25 in the first thesis, and Cases 4 and 5 in the second thesis, as presenting inadequate data regarding patency of arteries. Several of these cases are probably bona fide instances of Raynaud's disease. In an additional 4 cases (Cases 3 and 12 of the first thesis, and 2 and 6 of the second thesis) pulsations were diminished or absent in the peripheral arteries. Doubtless more cases could be added to this group if we included those in which palpation of the peripheral arteries, for pulsation, was inadequate. In several instances, Raynaud wrote, "pulsations were perceptible," but he did not designate which arteries were palpated or whether pulsation was diminished. We know that gangrene due to arteriosclerosis or thrombo-angiitis obliterans may occur in the presence of normal or slightly diminished pulsations in some of the peripheral arteries. The incomplete observations, and the failure to recognize diminution in pulsation as evidence of organic disease of the arteries, doubtless led to his statement: "The absence of arterial occlusion has only a negative value and also applies to diabetic gangrene" (page 98).

Case 3 in Raynaud's first series deserves special consideration. A young soldier had had dropsy at the age of 16 years and had been short of breath thereafter. On the night of admission to the hospital numbness of the left arm developed, the radial pulse was barely palpable, and the extremity was white and cold. Five days later, a similar condition developed in the right arm. Raynaud's assumption that the cause of the disturbance was a functional lesion which extended from the capillaries to the arteries, that is, to a spasmodic state of the arteries, appears unwarranted. The history of edema, dyspnea, and sudden onset of distress in first one and then the other arm, with diminished or absent pulsation in the

radial arteries, almost certainly represents arterial embolism, probably of cardiac origin.

It is perhaps understandable how such a brilliant investigator, presenting evidence of gangrene without organic occlusion of the arteries, could fail to record the status of the peripheral vessels, for some of the records were collected from the literature and the patients were never seen by Raynaud (page 31). Only 5 of the 25 cases presented in 1862 were Raynaud's own cases, but careful scrutiny of the records of these 25 cases indicates that he probably observed an additional 5, a total of 10, or less than 40 per cent of all cases the records of which are given. In 3 of these 10 cases, however, the state of pulsation in the peripheral arteries is not given. In the second thesis Raynaud presented 6 cases, all of which he observed personally; there were 2 in which absent or diminished pulsations were noted and 2 in which the state of pulsations was not given.

If one examines closely the significance of the term gangrene as used by Raynaud, one finds an entirely different connotation than that of many later authors. Raynaud described loss of tissue localized to the ends of the digits and wrote: "Symmetrical gangrene is mostly limited to the skin . . . small phlyctenulae always on the ends of the digits . . . the most profound gangrenes (are) those which go to the length of causing the fall of many ends of fingers or toes." He differentiated clearly (page 113) senile gangrene (which is due to an occlusive arterial lesion the same as it is in thrombo-angiitis obliterans) and symmetrical gangrene of Raynaud's disease; yet many cases of so-called Raynaud's disease in contemporary literature are obviously examples of occlusive arterial lesions. The reason for this confusion must in part be laid at Raynaud's door because the gangrene described in several of his cases varied greatly from that described in his original definition. In his first thesis, in Case 13 there were lesions on the heels, and in Case 14 the ends of some fingers, to the first joint, had been lost. In Case 16, there was complete gangrene of the ends of the fingers and toes, to the second phalanges, and amputation was necessary. In Case 17 dry gangrene of all fingers and toes was present; in Case 18, gangrene of both feet; in Case 19, ulcers on the legs and sloughs on the dorsum of the feet; in Case 21, all toes and many fingers had been lost with gangrene; in Case 22, dry gangrene extended as high as the elbows and as high as the ankles, and there was gangrene of cheeks and miliary eruptions over the body; in Case 23, there was gangrene of the entire left hand, shoulders, thigh, etc; in Case 24, gangrene of many fingers and of both feet had resulted in spontaneous amputation; in Case 25, both arms were gangrenous to the elbows. In the second thesis, in Case 6, the patient had suffered spontaneous loss of the toes from gangrene. Here, then, are 12 cases, in each of which the gangrene far exceeded

in degree and extent that described by Raynaud as the maximal gangrene which might occur in the disease he was describing. In these 12 reports, the state of the pulsations in the peripheral arteries was recorded in only 2; namely, in Case 18 (first thesis) in which freezing as an etiologic factor could not be excluded, and in Case 6 (second thesis) in which there was definite arterial occlusion. This group is comprised of two-thirds of the total 18 cases in which pulsations in the peripheral arteries were diminished, absent, or not mentioned. They can all be excluded from any consideration of Raynaud's disease because in 7 cases the gangrene exceeded in extent and severity that which Raynaud described as being characteristic of the disorder on which he was writing and because the state of pulsations in the arteries was diminished, absent or not mentioned.

Case 11 (first thesis) was probably an example of scleroderma with vasomotor changes, but otherwise it meets the requirements laid down by Raynaud.

Raynaud is hardly consistent as regards symmetry of gangrene, for he wrote that the gangrene displays "remarkable tendency to symmetry;" that it "always affects symmetrical parts;" that it involves "symmetrical parts which become affected together in the great majority of cases" and that "some (cases) deviate from the type (symmetry) more or less." This uncertainty is well illustrated, for Cases 4, 10, and 3 of the first thesis, and Case 6 of the second thesis present asymmetry. That all of these cases were authentic examples should be questioned. In Case 4 there was only recurrent syncope, and the condition of pulsations in the arteries was not given; cervical rib was not excluded. In Case 10 there was only a dry slough on the extremity of one toe, with no preceding changes in color. Case 3 had been discussed already as an example of arterial embolus of cardiac origin, and in Case 6 of the second thesis there was extensive gangrene and arterial occlusion. There seems adequate basis, other than asymmetry, in each case, to exclude it from consideration as an example of the type of disease Raynaud described in the text of his two theses.

There remains, however, a practical certainty that the condition which should be known as Raynaud's disease is always bilateral, and this conforms to our observations of more than 150 cases. Moreover, this bilaterality must indicate simultaneous involvement of symmetrical parts, for Raynaud described the phenomenon of "(symmetrical parts) affected together" and "the tendency (of the gangrene) to localize itself at the same time to the right and left halves of the body." Emphasis must be laid here on the words "together" and "at the same time." Obviously it was not Raynaud's intent that the term symmetrical gangrene should apply to gangrene occurring in one extremity weeks or months before involvement of its homologous member of the opposite side. This

should be borne in mind when speaking of symmetrical gangrene. He intended the word "symmetry" to connote simultaneous symmetrical involvement. It is apparent that close adherence to this tenet of simultaneous symmetry alone would obviate a large share of the confusion which surrounds the diagnosis of Raynaud's disease.

In 16 of the cases (53 per cent) presented by Raynaud in both theses taken together, intermittent changes in color were not exhibited. All of these could be eliminated on other grounds: asymmetry, too extensive gangrene or a failure to note the presence or absence of pulsations in the peripheral arteries.

TABLE 1.—CASES REPORTED BY RAYNAUD WHICH DID NOT CORRESPOND WITH THE SYNDROME DESCRIBED BY HIM.*

Case.	Features not characteristic of Raynaud's syndrome.			
	Asymmetrical abnormalities present.	Gangrene of excessive degree or extension present.	Arterial pulsations absent, definitely diminished, or not reported.	Intermittent color changes absent.
First thesis:				
1	Yes	
2	Yes	
3	Yes	..	Yes	Yes
4	Yes	..	Yes	
5	Yes	
7	Yes	Yes
10	Yes	Yes
11	(scleroderma)		
12	Yes	Yes
13	Yes	..	Yes
14	Yes	..	Yes
16	Yes	Yes	Yes
17	Yes	Yes	Yes
18	Yes	..	Yes
19	Yes	..	Yes
20	Yes	Yes
21	Yes	Yes	Yes
22	Yes	..	Yes
23	Yes	Yes	Yes
24	Yes	Yes	Yes
25	Yes	Yes	Yes
Second thesis:				
2	Yes	
4	Yes	
5	Yes	
6	Yes	Yes	Yes

* Cases 6, 8 and 9 of Raynaud's first thesis and Cases 1 and 3 of his second thesis corresponded with the syndrome described by him. Case 15 of the first thesis may have corresponded with the syndrome, but whether or not it fulfilled the condition of displaying intermittent color changes is questionable.

Critical examination of Raynaud's cases, then, on the basis of essentials laid down in the text of his theses, requires us to exclude (Table 1) all but 6 (Cases 6, 8, 9 and 15 of the first thesis, and Cases 1 and 3 of the second thesis). In addition, Cases 1 and 2 of his first thesis and Cases 2, 4 and 5 of his second thesis fill all the require-

ments for the diagnosis of Raynaud's disease except that the state of pulsation in the peripheral arteries is not noted. Some of them, particularly Cases 1 and 2 of the first thesis, are probably instances of a mild type of the affection. In Case 2 of the second thesis the radial artery was diminished in caliber during an attack of change in color. This may occur when Raynaud's disease or when organic arterial disease is present.

When the acceptable cases are examined to determine their common symptoms, it is seen that all 6 were personally observed by Raynaud. Paroxysmal attacks of pallor, or cyanosis, or both, were noted in all instances. This is important, for intermittency of changes in color was not used by us as a basis for accepting these cases as true instances of the disease which Raynaud was describing. Of the 25 cases excluded as not being typical of Raynaud's disease, excluded, that is, on the basis of considerations other than intermittency of changes in color, in 16 (64 per cent) intermittent changes in color were not noted. In Case 1 of the second thesis, visual disturbances, with narrowing of the retinal arteries, were observed during or shortly after evidence of the attack as seen in the extremities. Involvement of the nose or ears by cyanosis was observed in three instances (Cases 8, 6 and 15, first thesis). Exposure to lower temperature as the immediate cause of the attacks of cyanosis or pallor was noted in Cases 1 (second thesis) and 6 (first thesis).

In the 6 acceptable cases, 5 patients were women, aged 22, 27, 28, 30 and 52 years, respectively; the man was aged 59 years.

Now, after a critical survey of Raynaud's cases and the material in the text of his two theses, we may proceed to the definition of the disease named after Raynaud. His own special criteria are as follows: "In slight cases the fingers and toes become cold, cyanosed and livid and at the same time more or less painful. In grave cases the area affected by cyanosis extends upward for several centimeters above the roots of the nails; at the same time the nose and ears may become the seat of analogous phenomena. Finally, if the state is prolonged for a certain time, we see gangrenous points appear on the extremities; the gangrene is always dry and may occupy the superficial layers of the skin from the extent of a pin's head up to the end of a finger, rarely more. That which gives to this malady its special feature is the remarkable symmetry which the lesions manifest. . . . This interesting peculiarity taken with intermittency of attacks in many cases would in itself justify the belief that there exists no material obstacle to the course of the blood in the arteries." Here is the meat of Raynaud's entire presentation, a definition which, as has been shown, excludes many of his cases. Close adherence to the fundamentals laid down in this definition would eliminate the confusion which has existed, and the definition demonstrates clearly that most cases in the literature are not of a type that would meet the description given by Raynaud. Unfortunately, cases

reported by Raynaud have too often served as models for later authors without due consideration of the fact that many of Raynaud's cases did not meet the fundamental tenets of his researches. Too much weight has been given to the words "gangrene symmetrique" in the title of Raynaud's first thesis, in spite of the fact that the full title reads "L'asphyxie local et de la gangrene symmetrique." Raynaud later attempted a correction of this error, for he wrote in his thesis of 1874: "May I now be allowed to criticize the name which I gave the disease . . . local asphyxia and symmetrical gangrene are not two distinct maladies but two degrees of the same malady . . . the second is often absent."

The loose application of the term "Raynaud's disease" has been emphasized by Cassirer, who wrote:* "Those who have reported cases of this kind since Raynaud, have not by any means limited themselves to inclusion of the important characteristics of the affection, which were given by Raynaud. Cases have been described particularly by English authors, which had hardly a single characteristic in common with those originally given by Raynaud; symmetry and preceding vasomotor appearances were absent; the vascular system was not intact; the gangrene occurred in the course of an infectious disease and spread widely and much more."

Raynaud's disease in men and children is rare in our experience; yet it is commonly reported. In order to demonstrate the type of case which has crept into the literature under the title of Raynaud's disease, we present a study of 25 unselected cases in men or children from the German, English, and American literature (Table 2). In these 25 cases, the condition of the pulsation in the peripheral arteries was not noted in 18, was normal in 1, and absent or markedly diminished pulsations were noted in 7 cases. Consideration of these 25 cases from the standpoint of simultaneous, symmetric involvement, with discoloration or gangrene, reveals the following: symmetry was present in 13 cases, absent in 11 cases and not noted in 1 case. Gangrene was present in 15 of the 25 cases but exceeded the maximum described by Raynaud in 10 cases. Frequently the gangrene had been so extensive that amputation of a leg at the mid-femoral region had been necessary. Cyanosis or pallor was described in 15 of the cases, of which 9 had constant changes in color and 6 intermittent changes in color. Posture influenced the color markedly in 2 cases in which changes in color were intermittent. In 1 case, change in color appeared only when the patient was using a pneu-

* "Diejenigen die nach Raynaud über derartige Krankheitsfälle berichtet haben, haben sich in ihren Diagnosen keineswegs immer an diese von Raynaud gegebene Feststellung der wichtigsten Züge der Affektion gehalten; und es sind, namentlich von englischen Autoren unter dem Namen Raynaudsche Krankheit Fälle beschrieben worden, die kaum noch einen Zug mit dem ursprünglichen Krankheits-bilde der Raynaudschen Affektion gemeinsam hatten: da fehlte die Symmetrie und die vorausgehenden vasomotorischen Erscheinungen; das Gefäßssystem war nicht intakt, die Gangrän trat im Laufe einer Infektionskrankheit auf, dehnte sich weit aus, und anderes mehr."

TABLE 2.—SUMMARY OF TWENTY-FIVE UNSELECTED CASES FROM GERMAN, ENGLISH AND AMERICAN LITERATURE WHICH WERE PRESENTED AS EXAMPLES OF RAYNAUD'S DISEASE IN MEN OR CHILDREN.

Age (years) and sex.	Clinical history.	State of pulsations in peripheral arteries.	Probable diagnosis.*
32 (M) (M)	Right hand cyanotic; left hand blue and cold, with impending gangrene Two months of swelling and stiffness of hands; hands to above wrists stony and wooden with fixation of joints; crater-like ulcers on finger tips Two years of severe pain in leg and foot; varicose veins and superficial phlebitis; gangrene of great toe, with edema of lower third of leg Amputation of both legs for gangrene; uncontrolled diabetes	Absent in left radial, markedly diminished in right radial Not mentioned	Thrombo-angiitis obliterans Scleroderma
32 (M)		Not mentioned	Thrombo-angiitis obliterans
60 (M) Child (F)	Chorea with involvement of heart; auricular fibrillation; sudden pain in left foot with pallor and coldness; similar events in right foot the following day; gangrene of right foot with amputation Local asphyxia of fingers of left hand with gangrene of last phalanx of index finger and tip of third finger Weakness and tingling of right hand; pallor of hand with elevation or immersion in cold water; cyanosis when dependent	Absent in dorsalis pedis and posterior tibial bilaterally Not mentioned	Arteriosclerotic or diabetic gangrene Embolism of cardiac origin
43 (M) 45 (M)		Not mentioned	Thrombo-angiitis obliterans
48 (M)	Between 1906 and 1914 amputation of right first and fifth toes, right foot, right leg, left first, second and third toes, right first, second and third fingers for gangrene and pain Pallor and coldness of index and middle fingers when using pneumatic stone cutter which vibrated 900 to 1000 times each minute	Absent in right radial and ulnar diminished in right brachial and subclavian Not mentioned	Thrombo-angiitis obliterans with vasomotor changes Thrombo-angiitis obliterans
26 (M)		Not mentioned	Vasomotor changes effected by rapid vibration
40 (M) 37 (M) 38 (M) 51 (M)	Pains in fingers and toes, with swelling and lividity; fingers and toes numb; tips of fingers and toes black Amputation of left first and fifth toes for gangrene and pain; ulcer on left third toe; fingers and toes blue at times Attacks of pallor and cyanosis of fingers; amputation of left first and second toes for gangrene and pain; no healing "Typical" fingers and toes with high-grade ischemia and anesthesia of digits	Not mentioned Not mentioned Slight, bilaterally in dorsalis pedis Not mentioned	Thrombo-angiitis obliterans Thrombo-angiitis obliterans Thrombo-angiitis obliterans with vasomotor changes Insufficient data

Child 9 days	Cyanotic at birth; blisters on mouth, gangrene of all extremities; necropsy disclosed intra-auricular septal defect, and stenosis of isthmus of aorta; arteries and veins of extremities appeared normal	Pulsations not mentioned; arteries normal at necropsy	Congenital heart disease and unknown factors
34 (M)	Pain in right foot and leg for three years while walking; pain in left fifth toe; removal of toenail with no healing; superficial phlebitis; death after Leriche operation; necropsy not done	Not mentioned	Thrombo-angiitis obliterans
(M)	Froze both feet 5 years before report was made; for 3 years previous to report feet had tired easily; amputation of right leg for pain in the right foot; pain in the right hand and cracking of skin on finger tips, with gangrene	None in either radial.	Thrombo-angiitis obliterans
33 (M)	Six years previous to report right great and left second toes sloughed after severe pain and gangrene; 1 year previous to report, right and left middle fingers painful, swollen and gangrenous; right middle finger amputated	In dorsalis pedis and radial bilaterally, varied from absent to normal; pathologic changes in arteries of amputated finger	Thrombo-angiitis obliterans
36 (M)	Blueness of ears, fingers, hands and legs to the knees; multiple areas of cutaneous gangrene over shoulders, arms, forearms, hands, fingers, hips, knees, legs, toes and scrotum	Not mentioned	Indeterminate
40 (M)	Dermatitis herpetiformis for 1 year; then brown, anesthetic spots on two distal phalanges of right middle finger; 6 weeks later, recurrent attacks of cyanosis and pallor of all finger tips on left hand; later dry gangrene in these regions	Not mentioned	Indeterminate
60 (M)	Pain and blueness of fingers; cracks around finger nails; rheumatic pains in arms and mottling of skin of both forearms; at necropsy, carcinoma of stomach with metastasis to inferior cervical ganglion found	Normal in dorsalis in pedis and radial, bilaterally	Indeterminate
35 (M)	Amputation of right first and second toes, and 2 fingers for pain and gangrene, very slow healing; amputation of left first and right third toes, no healing	Not mentioned	Thrombo-angiitis obliterans
39 (M)	Cyanosis, pain and coldness in extremities for 3 years; color relieved by elevation, increased by dependency; ulcer on left great toe for 6 months	Not mentioned	Thrombo-angiitis obliterans
39 (M)	Four months of purple discoloration of hands with gangrene of left first and third fingers; severe pain	Not mentioned	Thrombo-angiitis obliterans
41 (M)	Rust-red discoloration of fingers followed by swelling and pain; both great toes swollen and tender with gangrenous areas on each; severe pain	Not mentioned	Thrombo-angiitis obliterans
33 (M)	Angina pectoris and intermittent claudication	Not mentioned	Thrombo-angiitis obliterans with involvement of coronary arteries

matic tool, in another it appeared usually in the morning, in 1 case it was noted with exposure to cold, and it appeared spontaneously in 1 case.

Many cases were obviously instances of peripheral occlusive arterial disease, and in the history intermittent claudication had been noted or suggested, as well as superficial phlebitis and absence of pulsation in the peripheral arteries.

Our tentative diagnoses, made from the histories and observations given in the reports, are distributed as follows: thromboangiitis obliterans, 16 cases; unknown, 4; arteriosclerosis, 1; embolism, 1; vasomotor changes associated with rapid vibration of extremity while using a pneumatic tool, 1; congenital heart disease, 1; multiple cutaneous gangrene (not limited to extremities) with cyanosis of extremities, 1, and Raynaud's disease, none.

It is admitted that diagnoses made from reports of cases, without the privilege of examining the patient, are subject to a high error, but the finding that none of these 25 cases fulfills the requirements laid down in Raynaud's theses is pertinent. It is admitted that some of the cases simulate some of those described by Raynaud, but, as previously pointed out, many of Raynaud's cases did not meet his own minimal requirements. In fact, he characterized many of them as questionable or undefined types of cases.

Comment. Since Raynaud made his classical description of the disease which bears his name, further clarification has been made in the group of peripheral vascular diseases. Thromboangiitis obliterans has been identified and accepted as an entity, and embolic occlusion of the peripheral arteries, gangrene and trophic changes due to medicaments are better recognized. Of significance is the recognition that vasomotor symptoms are more often secondary phenomena than primary. These symptoms frequently accompany organic disease of the arteries; hence, vasomotor disturbances only do not constitute a diagnosis of Raynaud's disease. It is admitted that our knowledge is still defective, and cases occasionally do not permit of accurate differentiation or classification. Such a case should be presented as an unusual or atypical case and not given the name of a condition to which it obviously does not belong. Some of these cases may represent new or previously undescribed syndromes.

It is obvious that confusion and not advancement of knowledge is served by departing from the criteria stated by Raynaud. If this disease is to remain an entity, it must have some boundaries. Other explanations must be found for the cases which depart from the prescribed limits.

From our group of 150 carefully studied cases, in all of which complete neurologic examination was done and careful notation of the patency of the peripheral arteries was made and reexamined

after long intervals, we are convinced that there is a definite primary disease or disturbance which can be called Raynaud's disease. The minimal requirements for diagnosis are those originally stated by Raynaud: (1) intermittent attacks of discoloration of extremities; (2) absence of evidence of organic arterial occlusion; (3) symmetric or bilateral distribution, and (4) trophic changes, when present, limited to the skin and never consisting of gross gangrene.

Secondary criteria are as follows: (1) predilection for females, such that more than 90 per cent of cases appear in persons of this sex, and (2) absence of pain is so striking that severe pain during the attacks is exceptional, and its presence militates against the diagnosis of a primary vasomotor disturbance of the spastic type.*

In addition to these diagnostic requisites, exclusion of any primary disease that in itself can give rise to vasospastic symptoms is of primary importance. Arthritis, neuritis, cervical rib, thrombo-angiitis obliterans, arteriosclerotic disease, and other diseases, are at times associated with disturbances of color of the hands or feet. The large incidence of this disease in females makes its diagnosis in the male at best tentative. In our experience, in cases in which diagnosis of Raynaud's disease in the male has been made early, and in which these patients have subsequently been traced, evidence of organic occlusion of the peripheral arteries usually has been found. Likewise in cases of gangrene of greater extent than epidermal gangrene; that is, gangrene involving a digit, pathologic examination has disclosed thrombosis of the type which we recognize as thrombo-angiitis obliterans. In fact, gangrene in Raynaud's disease is relatively rare; probably in 20 per cent of cases the patients suffer definite loss of tissue, and this frequently consists of minute excavations without symptoms. The more severe grades of gangrene take the form of felons or suppuration of the digits, and frequently are associated with sclerodermal changes in the skin of the digits.

If the field of peripheral vascular diseases is to assume its rightful place among other branches of medicine, the same care must be manifested as that which brought order out of chaos in other fields and elevated them to their present high level. Adequate care in diagnosis is important not only from an academic standpoint, but from a practical standpoint as well. Inadequate examination is responsible for many errors in diagnosis. To diagnose Raynaud's disease without determining the state of pulsation in the peripheral vessels is comparable to diagnosing mitral stenosis without listening to the heart. Unless due caution is exercised, operative measures

* Lewis has, on the basis of careful experiments, postulated that Raynaud's disease does not have a vasomotor basis, but that a local fault of the digital arteries is the underlying disturbance. Simpson, Brown and Adson's work shows that in the early uncomplicated case, a vasomotor basis exists, but in the later or complicated case a local disturbance of the arteries is also present.

on the sympathetic nerves, which induce a high percentage of cures in properly diagnosed cases, may be subjected to undue criticism and fall into disrepute.

Conclusions. Raynaud described a clinical syndrome which justifiably bears his name. His requirements for diagnosis are valid and are borne out by our studies of more than 150 cases. These requirements are: (1) Gangrene or trophic changes limited in a large degree to the skin; (2) symmetrical or bilateral involvement; (3) absence of evidence of occlusive lesions of the peripheral arteries, and (4) intermittent attacks of changes in color which usually precede the trophic changes by months or years.

Many of the cases reported by Raynaud were not illustrative of the condition described by him, as is usually the case with eponymic diseases described many years ago. They did not fulfill the minimal requirements. The use of these cases as models by many subsequent authors has led to a high percentage of erroneous diagnoses.

Study of 25 cases reported in the literature as Raynaud's disease shows that none of them fulfills the necessary requirements for such a diagnosis. These cases are characterized by failure to adhere to Raynaud's basic requirements, and inadequacy of examination of patients. Many of the cases are obviously examples of thrombo-angiitis obliterans.

Accurate diagnosis in peripheral vascular disease is essential if treatment is to be properly evaluated.

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ERYTHREMIA AND MYELOGENOUS LEUKEMIA.

REPORT OF CASES PRESENTING ASPECTS OF BOTH DISEASES.

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WHILE there is generally little difficulty associated with the diagnosis of erythremia, there are cases reported in the literature which present a composite picture of both polycythemia and myelogenous leukemia. In these instances it is often exceedingly difficult to make a differential diagnosis. Indeed the answer is, more often than not, in doubt until after the postmortem examination.

Pendergrass and Pancoast,¹ Minot and Buchman,² Harrop³ and A. Horstrup⁴ have reviewed the literature and considered the significance of the composite picture of polycythemia and myelogenous leukemia.

The first case is reported because of the unusual blood picture, the course during treatment, and the postmortem findings. Besides 36 cases of myelogenous leukemia and 11 cases of erythremia appearing in the records of the Peter Bent Brigham Hospital, there are 4 others which combine features of both diseases. The records of these also are presented briefly.

Case Reports. CASE 1.—W. J. G. (P. B. B. H. Med. 36155), aged 50 years, white, single, Canadian-American, refrigerator engineer, entered the hospital December 20, 1929, complaining of pains in the knees, calves and feet of 4 months' duration. Twenty years before admission he suffered a depressed fracture of the skull, from which an uneventful recovery was made. Four months before entry the patient's knees became painful, red and swollen. Shortly after, an enlarged spleen was found. Three months before admission the right foot became painful, and numbness was noted in both feet for the first time. The numbness gradually extended upward to the knees. With it, he began to have shooting pains extending from the toes and feet into the calves of both legs. These were worse at night. Walking caused the soles of his feet and the lateral aspects of both knees to pain. Since the onset of the present illness he has lost 30 to 40 pounds, weighing 127 pounds on admission.

Physical examination revealed a well-developed, undernourished, white male. He was mentally clear. The face had a florid, erythremic appearance with a suggestion of right facial weakness. The lips, nail beds and tongue were slightly cyanotic. The skin was warm and florid. There was a small, irregular depression in the left parietal region of the skull. The fundi were not unusual; the vessels were not turgid, nor the retina more

colored than normal. The diaphragm was high on the left side, giving dullness at the base of the lung in front, back and axilla, approximately 2 interspaces higher than normal. Posteriorly there were medium, crepitant râles at the left base on deep inspiration. Stereoscopic Roentgen ray examination showed the lungs to be clear. The diaphragms were dome-shaped, with the left diaphragm limited fluoroscopically. Stereoscopic Roentgen ray examination of the lumbar spine and pelvis revealed no abnormality. The heart and peripheral vascular system were not remarkable. The blood pressure was 120 systolic and 90 diastolic. The entire left half of the abdomen was filled with a firm, nontender, smooth mass, presumably the spleen, which pushed up the diaphragm, extended down below the anterior superior spine of the pelvis and a short distance across the midline to the right. The liver did not appear enlarged. There was no lymphadenopathy. The reflexes were normal. Hyperesthesia of the soles of both feet was present. Using a G-48 tuning fork, vibratory sensibility

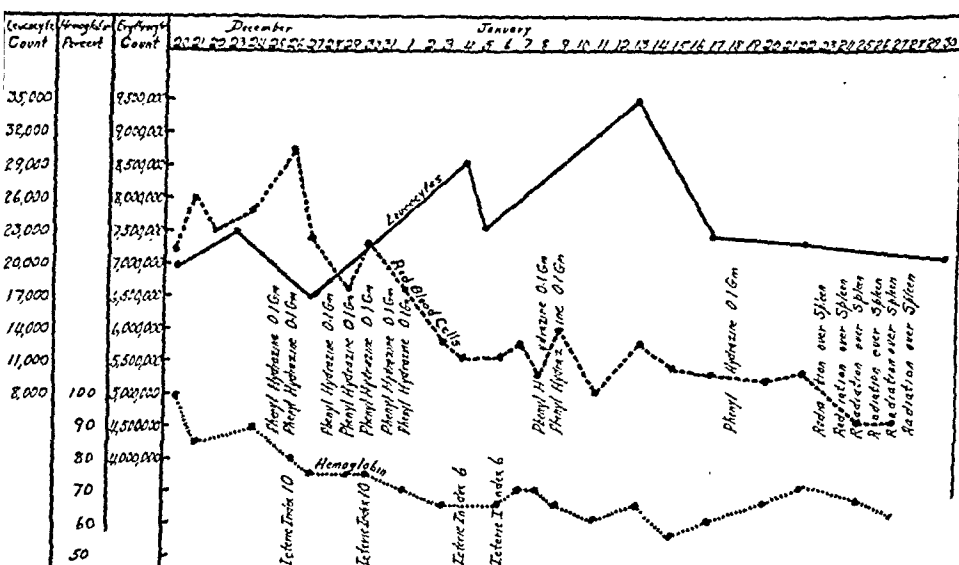


CHART I.—Case 1. Variations of blood elements in relation to treatment.

was lost in both legs but present in both iliac crests. Position sense, pain and touch seemed normal in both legs. There was no ataxia.

The urine occasionally showed a few hyalin and finely granular casts. The specific gravity ranged between 1.014 and 1.018. The phenolsulphonephthalein test gave an excretion of 60 per cent in 2 hours and 10 minutes in 300 cc. of urine. The stool examination was negative. Gastric analysis, using the Ewald test meal, revealed no free hydrochloric acid, and total acidity ranging between 15 and 22 units of 0.1-N sodium hydroxid in specimens of a fractional test. There was a positive benzidin reaction for occult blood in 4 of the 5 specimens.

Blood Studies. The Wassermann, Hinton and modified Hinton reactions were negative. Blood culture was negative. Clotting time by the 6-tube method was 15 minutes (normal control 6 minutes). The bleeding time was 2½ minutes by the method of Duke. Platelet count was 740,000 (Wright and Kinnicutt method). Fragility test: beginning hemolysis in 0.46 per cent NaCl; complete hemolysis in 0.28 per cent at the end of 2 hours. At the

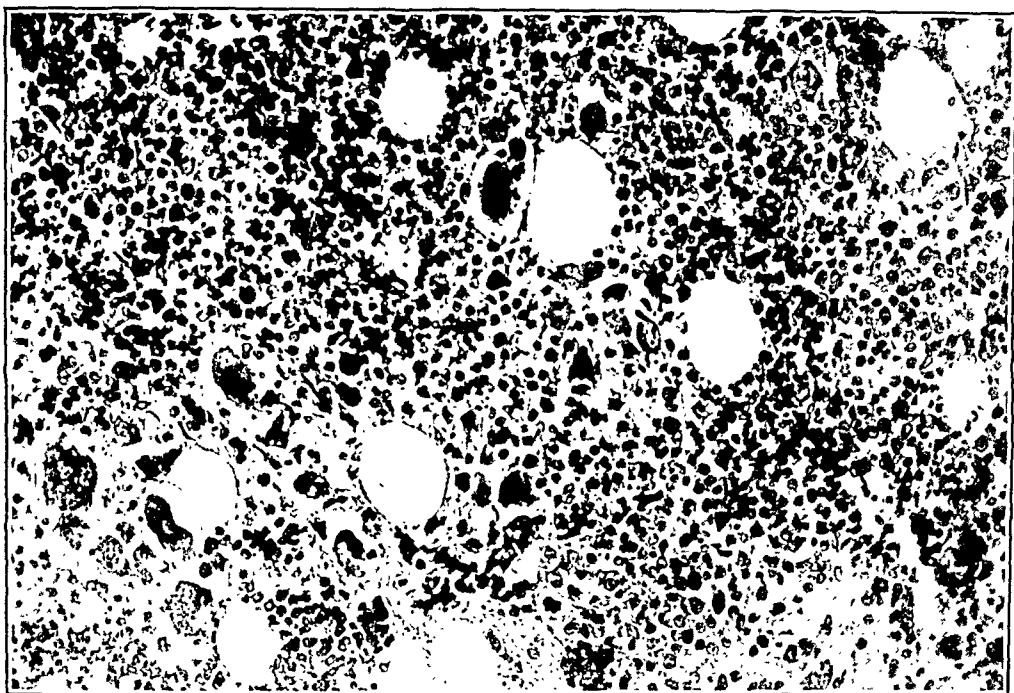


FIG. 1.—Case 1. Bone-marrow from femur. The section shows congestion of the marrow, scarcity of fat, hyperplasia of erythropoietic and leukocytic elements, and numerous megakaryocytes. $\times 300$.

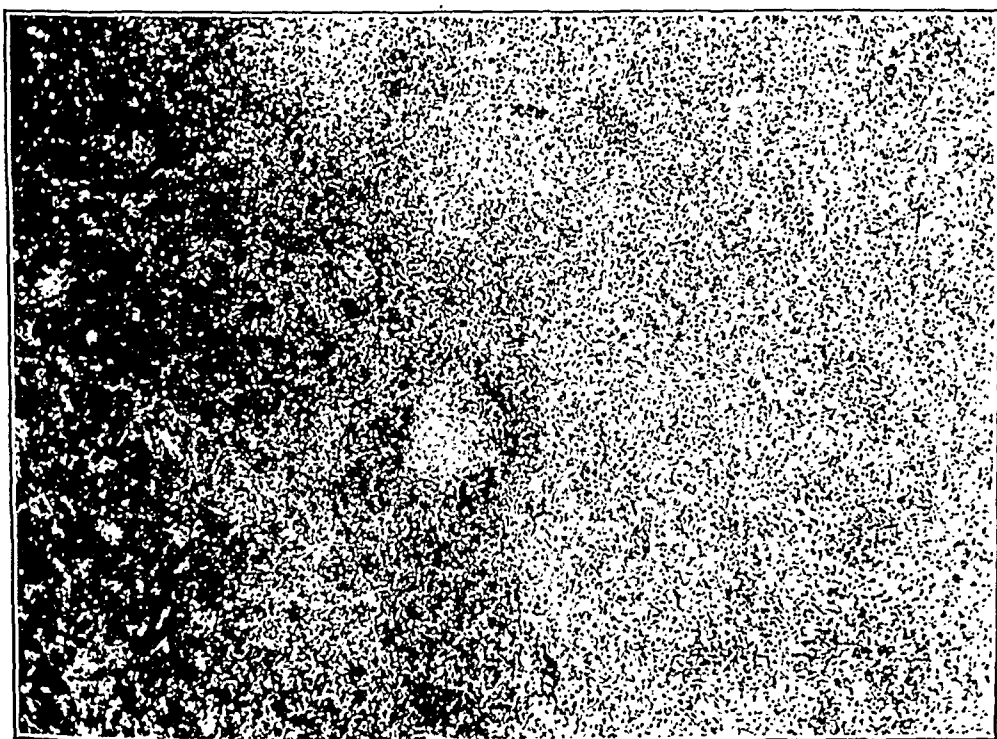


FIG. 2.—Case 1. Spleen. Congestion and diffuse fibrosis with prominence of trabeculae and diminution of the lymph follicles is shown. The dark area at the left represents hemorrhage. $\times 110$.

end of 10 hours: beginning hemolysis in 0.50 per cent; complete hemolysis in 0.28 per cent. Normal control: beginning hemolysis in 0.46 per cent; complete hemolysis in 0.30 per cent at the end of 2 hours. After 10 hours, beginning hemolysis in 0.46 per cent and complete hemolysis in 0.38 per cent. The variation in hemoglobin, red cells, white cells, and icteric index in relation to treatment with phenylhydrazine and Roentgen rays are depicted on the chart.

The hematocrit findings were as follows:

	R. B. C. count.	Cells, per cent.	Plasma, per cent.	Indiv. cell vol. 10-11 cu.cm.,
December 22 . . .	7,585,000	53.3	46.7	7.1
December 26 . . .	6,900,000	52.8	47.2	7.6
January 3 . . .	7,900,000	53.8	46.2	6.8

The differential blood counts and the results of the study of the blood smears are summarized in Table 1.

Clinical Course. On admission the patient's temperature was 98.8° F. and the pulse rate was 65. On the evening of December 23 the patient's temperature rose to 99.5° F. The next morning it was normal. He was given the first dose of 0.1 gm. phenylhydrazin. That evening the temperature began rising, reaching 102° F. on December 25. There was no jaundice nor rise in the icteric index. By December 27 the temperature had returned to 99° F. and the administration of phenylhydrazin was resumed without untoward effects. The excruciating pains in his knees and calves, complained of on admission, continued. On account of the fall in hemoglobin and red count the phenylhydrazin was discontinued for a week, beginning January 1. Beginning about January 17 it was noted that the pain in his legs was abating. During the course of treatment with phenylhydrazin it was noted that the florid, erythremic appearance was gradually disappearing, giving way to a progressive pallor. The spleen showed a definite decrease in size, although on January 23 it was still below the umbilicus. On January 23 a course of Roentgen ray therapy was commenced. This consisted of a maximum suberythema dose over the splenic area anteriorly and posteriorly. This is calculated as 750 "r" measured in air with a Duane ionization chamber, and is given in 6 divided doses of 250 "r" each on 6 successive days. On January 29, after having received the course of 6 Roentgen ray treatments, he suddenly became mildly disoriented. He complained of excruciating pains shooting down his legs and began having seizures of generalized trembling, spasmodic movements and stiffening of the entire body. These attacks continued for 24 hours. The suggestive right facial weakness found on admission became more pronounced. His pulse gradually became slower and weaker and on the evening of January 30 he died.

Postmortem Examination. The general appearance of the body was essentially normal. The heart weighed 360 gm. and was essentially normal. The lungs showed moderate congestion and edema, obsolete tuberculous lesions at both apices, but no evidence of bronchopneumonia or emphysema.

The spleen weighed 1220 gm. Its consistency was very soft. The capsule was thickened, smooth, moist and glistening, with numerous irregular, firm, yellow areas, representing old infarcts. The parenchyma was soft, pultaceous and of a uniform dull-red color with a tinge of pale gray, suggesting the color of ordinary red brick. No characteristic splenic markings were recognizable. On microscopic section (see photomicrograph) the spleen showed primarily fibrosis, congestion with scattered areas of hemorrhage and infiltration with abnormal types of cells. The Malpighian corpuscles were completely obliterated by the congestion and diffuse overgrowth of connective tissue. Rarely a cluster of lymphocytes was seen

TABLE 1.—CASE 1. BLOOD COUNTS AND BLOOD SMEARS IN A CASE OF ERYTHREMA.

Date.	Red blood cells and hemoglobin.	White blood cells.	Poly-morpho-nuclears, per cent.	Lympho-cytes, per cent.	Mono-cytes, per cent.	Eosino-phils, per cent.	Baso-phils, per cent.	Abnormal white cells, per cent.	Red cells.
December 20, 1929	7,230,000 100%	19,800	40	8	0	5	0	Metamyelocytes, 28 (N, 19; E, 6; B, 3) Myelocytes, 10 (N, 7; E, 3)	Moderate achromia; moderate anisocytosis and poikilocytosis; platelets increased.
December 21, 1929	8,070,000 85%	23,000	53	9	1	8	0	Metamyelocytes, 9 Myelocytes, 3 Unclassified smudges, 11 Myelocytes, 4	As above; 2 nucleated red blood cells.
December 27, 1929	7,420,000 75%	16,800	65	10	2	4	4	Unclassified smudges, 11 Metamyelocytes, 10 Myelocytes, 7	As above; 1 nucleated red blood cell seen; reticulocytes 0.8 per cent.
January 4, 1930	5,520,000 65%	29,200	67	5	1	4	6	Myelocytes, 9	Moderate achromia; marked anisocytosis and poikilocytosis; no nucleated red blood cells; platelets increased.
January 13, 1930	5,730,000 65%	34,300	65	10	2	8	6	Myelocytes, 9	As above.
January 22, 1930	5,350,000 70%	21,500	64	1	1	1	7	Young polys, 10 Metamyelocytes, 8 Myelocytes, 7 Myeloblasts, 1 Young polys, 27 Metamyelocytes, 7 Myelocytes, 2 Unclassified smudges, 7	Marked achromia; marked anisocytosis; young microcytes and macrocytes; many tail forms.
January 27, 1930	4,440,000 60%	10,000	46	0	2	6	3		As above; no macrocytes.

near a central artery, representing the remains of an old splenic follicle. The trabeculae were more prominent than usual due to the increase in connective tissue. The central arteries were sclerotic and not easily found. The infiltration of abnormal blood cells was the most significant feature of the microscopic picture. There were myeloblasts, neutrophilic and eosinophilic myelocytes, mature neutrophils, eosinophils and nucleated red blood cells. There were also many macrophages, endothelial leukocytes and a few large cells resembling megakaryocytes. The abnormal cells tended to occur in clusters or in small focal areas. Erythropoiesis was not a prominent feature.

The liver weighed 2255 gm. The gross appearance of the organ and capsule was normal. The cut surface showed a striking fine granularity. The parenchyma was softer and more friable than normal. There were no white spots indicative of leukemic infiltration. Sections of the liver showed marked congestion and infiltration of a few periportal spaces by lymphocytes, plasma cells and an occasional eosinophilic myelocyte. The dilated sinusoids and portal areas contained small numbers of leukocytes, resembling mostly neutrophils and myelocytes. There was, however, no typical leukemic infiltration, but an occasional island of erythropoiesis was seen. No mitotic figures were seen among the myeloid cells. In several periportal areas the connective-tissue stroma was increased and spread peripherally replacing parenchyma. Around the central veins there was, in some instances, a slight degree of fatty infiltration. There was no inflammatory reaction anywhere. The parenchyma was on the whole well preserved and, despite the congestion, the characteristic liver cords and lobules were distinctly seen. The gall-bladder was normal.

The thyroid gland, pancreas, gastrointestinal tract and pelvic organs showed engorged bloodvessels but were otherwise normal. The right kidney weighed 180 gm., the left 160 gm. They appeared normal. The sections showed no abnormalities nor evidence of leukemic infiltration. The adrenals were smaller than usual but were of normal shape and consistency. In one adrenal a small deep, brownish-red patch, which resembled a hemorrhage, was noted. Section of the adrenal glands showed several clusters of leukocytes composed of lymphocytes, plasma cells and young blast cells, possibly of the myeloid series. These groups of cells, situated in the medulla, were larger than those found in the liver and were more suggestive of a true leukemic infiltration. The bloodvessels were conspicuous owing to congestion.

The bone marrow from the femur, vertebrae, ribs and calvarium was hyperplastic and dull reddish-gray in color. On section (see photomicrograph) the bone marrow appeared congested. The bone spicules seen showed no degeneration nor defect in calcification. Only occasional fat cells were seen within the marrow. Numerous small clusters of cells with hyperchromatic nuclei and basic to eosinophilic cytoplasm representing areas of hematopoiesis were seen. Likewise there were numerous areas of myelocytes and their derivatives. Megakaryocytes were numerous and active. Eosinophils appeared to be present in greater number than in normal bone marrow. The histologic appearance was, however, not that which is usually found in leukemia, in that the myelocyte element was not excessive. To what extent, if any, the changes in the bone marrow have been influenced by phenylhydrazin and radiation is difficult to say.

The pathology of the brain was that of a diffuse hemorrhage into the subarachnoid space. The extravasation of blood was largely confined to the superior, lateral and medial aspects of the lobes of the cerebrum and cerebellum. There were no visible thrombi in the vessels. Most of the blood was found in the sulci and was of such diffuse distribution that it probably originated from the capillary bed. The arteries showed less sclerosis than

is generally found at the patient's age. There was a slight pressure cone on the inferior surface of the cerebellum. The ventricles were not dilated and they contained no blood in their cavities. The pons, medulla and cerebellum showed no hemorrhages into their substance. There were degenerative changes in many of the nerve cells of the cortex, but none were noted in the fiber tracts. The spinal cord showed massive hemorrhage into the subarachnoid space, similar to the brain, associated with which was edema and congestion of the cord and membranes.

Summary of Pathology. The pathologic picture was that of polycythemia with a terminal generalized subarachnoid hemorrhage of the brain and cord. The spleen weighed 1220 gm. and showed old infarcts, congestion, fibrosis and infiltration with abnormal cells. The bone marrow showed slightly greater hematopoiesis than normal, but there was no leukemic response on the part of the marrow. None of the organs, except possibly the adrenals, showed cellular infiltration suggestive of leukemia.

CASE 2.—F. P. (P. B. B. H. Med. 4444). A female, aged 66 years, entered the hospital complaining of a mass in the abdomen of 3 years' duration. Physical examination showed the general appearance suggestive of polycythemia, and an enormous spleen which filled the entire left side of the abdomen. Four blood examinations revealed an average red count of 4,903,000 (4,760,000 to 5,550,000) hemoglobin of 133 per cent (132 to 138) (NOTE.—These excessively high hemoglobin figures are questioned.) White count of 20,600 (20,100 to 21,700) and differential of polymorphonuclears, 81 per cent; lymphocytes, 1 per cent; monocytes, 14 per cent; eosinophils, 2 per cent; and basophils, 2 per cent. The smear showed 1 megaloblast and slight anisocytosis and poikilocytosis. The basal metabolic rate was 50 per cent above normal. Following discharge the patient lived 2 years. During the first year she received 22 Roentgen ray treatments over the spleen. Despite this treatment her red cell count mounted progressively, reaching a peak of 13,064,000 nine months after discharge. The hemoglobin varied between 95 and 132 per cent. The white count fluctuated between 12,000 and 24,000. Toward the end of the first year after discharge the red count began falling rapidly. Roentgen ray treatment was stopped but the red count continued to decline. The white cell count remained between 14,000 and 27,000. The differential count continued to show only a few myelocytes. Before death the counts were: red cells, 3,580,000; leukocytes, 28,000; hemoglobin, 68 per cent; differential cell count: polymorphonuclears, 37 per cent; young polymorphonuclears, 30 per cent; lymphocytes, 18 per cent; large monocytes, 8 per cent; basophils, 2 per cent; myelocytes, 5 per cent. Autopsy revealed typical myelogenous leukemia.

CASE 3.—(P. B. B. H. Med. 21587). A male, aged 37 years, entered the hospital because of swelling of the abdomen and pain in the left upper quadrant of 3 years' duration. Physical examination revealed emaciation, shifting dullness in the abdomen and the spleen 3 cm. below the costal margin. There was no erythema or cyanosis. Blood studies revealed hemoglobin, 126 per cent; red count, 6,430,000; white count, 49,000 with a differential of polymorphonuclears, 88 per cent; lymphocytes, 4 per cent; myelocytes, 8 per cent. The smear showed normoblasts and many immature leukocytes. The patient died 3 days after admission. Autopsy was not obtained.

CASE 4.—J. M. (P. B. B. H. Med. 7241). A white male, aged 61 years, entered the hospital because of a sense of pressure and swelling in the region of the spleen of 4 months' duration. Physical examination showed an erythematous appearance to the face and generalized adenopathy with several small firm nodes in the anterior axillary line. The spleen was 15 cm. below the costal margin. Before treatment the hemoglobin ranged between 95 and 125 per cent, averaging 107 per cent, the red count was 5,886,000

and the white count was 26,000. The differential showed 71 per cent polymorphonuclears, 6 per cent lymphocytes, 7 per cent monocytes, 11 per cent eosinophils, 5 per cent mast cells. The smear showed slight achromia, anisocytosis and a few macrocytes. Biopsy on one of the lymph nodes was reported as lymphoblastoma.

After receiving 78,688 millicuries of radiation over the splenic area, the spleen decreased slightly in size but the liver increased to 10 cm. below the costal margin. Under treatment, myelocytes began to appear in the blood stream. The hemoglobin fell to 80 per cent, the red cells rose to 7,360,000 and the white blood cells rose to 38,000. The average differential showed 62 per cent polymorphonuclears, 12 per cent lymphocytes, 4.3 per cent monocytes, 14.8 per cent eosinophils, 0.5 per cent basophils, and 5.5 per cent myelocytes. The patient died 3 months after admission. Before death the white count had fallen to 15,000 and the red count to 3,750,000. Despite the biopsy report of lymphoblastoma, a final diagnosis of chronic myelogenous leukemia was recorded.

CASE 5.—M. J. C. (P. B. B. H. Med. 37743), aged 45 years, white, single, Irish-American, woolsorter, entered the hospital because of severe abdominal pain of 4 days' duration. For 12 years the patient has had vague, intermittent, dragging upper abdominal pain relieved by soft and bland foods. Two years before admission, Roentgen ray examination showed a duodenal ulcer. Four days before admission the pain became unbearably sharp and aggravated by exertion.

Physical examination showed the appearance of the skin and mucous membranes characteristic of polycythemia. There was increased resistance and tenderness in the left upper quadrant of the abdomen where a firm mass extending three fingers' breadth below the costal margin was felt. The patient's temperature was elevated to 100° F.

Laboratory Studies. Roentgen ray studies of the gastrointestinal tract showed the stomach displaced to the right with pressure narrowing of the fundus, possibly due to an enlarged spleen. The duodenum showed a constant deformity suggestive of an ulcer. The urine and stool examinations gave negative findings. The Wassermann, Hinton and modified Hinton blood tests were negative. Gastric analysis after the Ewald test meal showed a maximum free acidity of 100 units of 0.1-N sodium hydroxid and a maximum total acidity of 130 units. The blood sugar was 101 mg. per cent., blood urea nitrogen, 21 mg. per cent; blood uric acid, 3.2 mg. per cent (old method); blood uric acid, 2.8 mg. per cent (new method); blood creatinin, 1.4 mg. per cent; blood phosphate, 4.3 mg. per cent; total proteins, 7.5 per cent; blood albumin, 4.4 per cent; blood globulin, 2.1 per cent; blood calcium, 10.6 per cent. Hematocrit cells, 61.2 per cent, plasma, 38.8 per cent; individual red blood cell volume 6.2 by 10^{-11} cc. The reticulocytes varied between 0.8 per cent and 1.6 per cent. Red cell fragility gave beginning hemolysis in a 0.38 per cent sodium chlorid solution. Hemolysis was not complete in a 0.28 per cent solution after 2 hours. The icteric index was 6. The bleeding time by the method of Duke was 1 minute and 30 seconds, the clotting time (capillary method), 2 minutes and 15 seconds. Platelet count was 320,000 (Wright and Kinnicutt method). Blood counts were as follows:

October 2: Hemoglobin (?) 75 per cent (Tallqvist); red cells, 7,700,000; leukocytes, 31,700. Differential: polymorphonuclears, 86 per cent; lymphocytes, 8 per cent; eosinophils, 3 per cent; myelocytes, 3 per cent. Red cells showed slight achromia. Platelets normal.

October 3: Hemoglobin, 158 per cent (Sahli); differential: polymorphonuclears, 88 per cent; lymphocytes, 5 per cent; large monocytes, 1 per cent; eosinophils, 1 per cent; basophils, 1 per cent; myelocytes, 4 per cent. Red cells normal.

October 5: Red cells, 8,610,000; leukocytes, 31,500.

October 8: Hemoglobin, 155 per cent (Sahli); red cells, 9,400,000; leukocytes, 28,500.

October 11: Red cells, 8,550,000; leukocytes, 45,500. Differential: polymorphonuclears, 91 per cent; lymphocytes, 5 per cent; large monocytes, 2 per cent; eosinophils, 1 per cent; basophils, 1 per cent. Red cells, normal.

October 17: Leukocytes, 44,000.

Clinical Course. The patient was placed on the Sippy régime. He continued to vomit and complain of increasing left upper quadrant pain. The possibility of a splenic infarct, or an infectious process was considered. On the sixteenth day after admission the pain became increasingly severe, the upper portion of the abdomen became tense and gave an impression of boggy fullness. The patient vomited bright red blood several times. There was marked vasomotor collapse and within a few hours the patient died. The course of events suggested the possibility of thrombosis of the splenic and portal veins with gastric hemorrhage as the cause of death.

Comment. A survey of the cases in the literature which present a combination of elements of both diseases suggests that:

1. In those cases which terminate as myelogenous leukemia, the disease generally starts with a phase suggestive of polycythemia. This polycythemia phase gradually disappears as the leukemic characteristics appear and grow more pronounced. Indeed, Naegeli⁴ believes that there is an initial polycythemia in the early stage of all cases of myelogenous leukemia.

2. In the cases of true erythremia the appearance of a marked leukocytosis with immature myeloid cells in the blood stream is generally a late manifestation and is evidence of a more profound disorganization of bone-marrow activity. This concept has been expressed by Minot² and Harrop.³

3. There may be a few cases which start out with the picture of myelogenous leukemia and undergo a progressive transition into true erythremia. Gheron,^{3,4} and Winter⁵ have reported such cases.

4. A case presenting the composite picture of myelogenous leukemia and polycythemia, or phases of each, is more than likely to be leukemia than erythremia. Thus, of 33 cases reviewed in the literature, 12 turned out to be leukemia and 5 erythremia. The remaining cases could not be classified, principally because they did not include postmortem examination. There were a few cases in which autopsy showed the presence of characteristics of both diseases, making differentiation impossible.

It is noteworthy that our patient died suddenly during the course of Roentgen ray treatment over the spleen. The question naturally arises as to whether there was any relationship between radiation and the sudden death. Horstrup⁴ points out the advisability of considering those patients with the combined picture as potentially poor risks for radiation. He cites only 1 case from the literature that was definitely improved by radiation over the spleen. Inasmuch as the disease runs a fatal course, often terminating suddenly,

and the appearance of immature myelocytic cells in the blood stream generally is a late manifestation in polycythemia, it is difficult to determine whether radiation actually hastens the end in this combined group. However, it is a possibility worth further consideration.

Summary. A case of erythremia presenting a marked leukocytosis, myelocytes in the blood stream, a huge spleen, and terminating fatally following Roentgen ray radiation therapy over the spleen, is reported with postmortem findings. Four similar cases appearing in the hospital records are reviewed briefly. A classification of cases having the combined picture of polycythemia and leukemia is suggested.

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PREGNANCY IN THE COURSE OF LEUKEMIA.

A CASE REPORT.

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THE number of reported cases of leukemia complicating pregnancy and of pregnancy occurring during the course of leukemia is small.^{1,2} Because of this fact; because of the lack of unanimity of opinion regarding the transmissibility of the disease to the child,^{1,3} because of the fact that pregnancy allowed to proceed to term is supposed to aggravate the leukemia and anticipate the fatal outcome;⁴ and because of the difference of opinion regarding the effect of deep radiation therapy on the function of the ovaries,^{5,6,7,8} we wish to report a normal pregnancy and delivery of a normal child occurring in a case of chronic myelogenous leukemia.

Case Report. R. B., female, white, nativity United States, aged 26 years, married, was admitted, October 22, 1928, and discharged, December 12, 1928.

Family History. Irrelevant.

Past History. Menstruation began at the age of 12 years; was of the 28-day type, not painful and apparently not excessive. The patient was married at the age of 18 years. She was delivered of a normal baby boy 9 months and 2 weeks from the date of her marriage. This pregnancy was characterized by the fact that nausea and vomiting began early in its course, that they were severe and that they persisted almost to up to the date of delivery. Menstruation occurred 5 months after this delivery. Two years and 9 months later the patient was delivered of a second normal baby boy. She had persistent, severe nausea, vomiting and headache during pregnancy. In the interval between these pregnancies, however, the patient felt perfectly well and carried on her household duties without difficulty. Menstruation recurred 7 months after this delivery.

Present Illness. About 15 months before admission the patient noticed that she tired easily. Progressive, severe and generalized weakness followed with head noises, headache and dizziness and blurring of vision. Her appetite became poor and the ingestion of food was accompanied by epigastric discomfort. The attacks of abdominal distress gradually became more frequent and protracted, so that they were present even when fasting. Later she complained of a diffuse swelling in the region of the thyroid gland.⁴ Subsequently shortness of breath developed which was aggravated by exercise and by the taking of food. About this time and quite by accident she felt a large mass (spleen) in the left upper abdomen. Bleeding from the gums and crops of purpuric spots occurred at first irregularly, but later rather frequently. Weakness, shortness of breath, abdominal distention and dragging sensation in the left upper abdomen finally became so severe that she applied for admission to the hospital for relief.

Physical Examination. There was diffuse, uniform enlargement of the thyroid; the gums were tender and bled easily on pressure; the lungs were essentially negative; the heart showed a soft, short systolic blow over the mitral area; the liver was enlarged about 1 inch below the free costal margin, smooth and not tender; the spleen was markedly enlarged, extending almost to the midline anteriorly and inferiorly to the level of the iliac crest; the inguinal and axillary lymph nodes were palpably enlarged, discrete and not tender. A few purpuric lesions were scattered over the skin of the lower extremities, but there were no leukemic nodules or diffuse leukemic infiltration of the skin. The neurologic status, excepting slight impairment of the vibratory sense in the toes, was normal.

Laboratory Data. Hemoglobin, 69 per cent, or 9.35 gm. (Dare); red cell count, 4.52 million; color index, 0.77; reticulocytes, 5 per cent; white cell count, 122,800. Differential count: Myeloblasts, 0; premyleocytes, 6 per cent; myelocytes, 12 per cent; metamyelocyte (I), 10 per cent; metamyelocytes (II), 18 per cent; neutrophils, 46 per cent; lymphocytes, 5 per cent; monocytes, 1 per cent; eosinophils, 2 per cent; basophils, 0. The platelets were numerous. Examination of the red cells in the stained film showed moderate qualitative changes. Coagulation time (Lee and White), 7 minutes; clot retraction good; bleeding time (Duke), 1 minute. Fragility of the red cells: Patient: Beginning hemolysis, 0.5 per cent sodium chlorid; complete hemolysis, 0.28 per cent sodium chlorid. Control: Beginning hemolysis, 0.44 per cent sodium chlorid; complete hemolysis, 0.32 per cent sodium chlorid. Van den Bergh: Immediate direct reaction, negative; indirect reaction, weakly positive. Icterus index, 9. The blood Wassermann test was negative (alcohol and cholesterin antigens). The blood sugar was 70 mg. per 100 cc. Urea nitrogen, 14.5 mg. per 100 cc. The

TABLE 1.—WHITE AND DIFFERENTIAL FORMULAE AND RADIATION THERAPY DURING PERIOD OF HOSPITALIZATION, OCTOBER 22, 1928, TO DECEMBER 12, 1928.

Date, 1928.	Erythrocytes.	Hemoglobin (Dare), per cent.	Grams.	Color index.	Reticulocytes, per cent.	Leukoocytes, thousands.	Myeloblasts.	Premyelocytes.	Myelocytes.	Metamyelocytes (I).	Metamyelocytes (II).	Neutrophils.	Lymphocytes.	Monocytes.	Eosinophils.	Basophils.	Radiation treatment.
Nov. 2 . . .	4.45	67	9.1	0.75	4.5	125.0	3	4	20	10	14	41	2	2	3	1	X A.S.
Nov. 9 . . .	4.10	66	9.0	0.80	5.0	83.8	2	5	14	11	16	45	2	1	2	2	X A.S.
Nov. 16 . . .	3.99	53	7.2	0.70	4.8	102.6	0	6	13	13	18	47	1	0	2	0	X A.S.
Nov. 27 . . .	4.33	52	7.1	0.60	5.8	98.0	0	7	14	5	13	52	3	3	1	2	X A.S.
Dec. 1 . . .	4.26	3.5	80.6	0	7	9	3	9	62	2	5	1	2	
Dec. 4 . . .	4.47	61	8.3	0.70	5.8	68.4	0	6	7	2	6	71	5	1	2	0	X A.S.
Dec. 10 . . .	5.25	62	8.4	0.60	5.0	40.0	0	5	9	9	13	54	2	4	1	3	

X A.S. = Deep radiation treatment over anterior spleen.

X P.S. = Deep radiation treatment over posterior spleen.

Details of radiation treatments are given under Treatment and Course in text.

urine was essentially normal. Bence-Jones bodies were not demonstrated. Urinary urobilinogen was normal throughout entire period of observation. The feces were negative for ova, parasites, pus, blood, excess mucus and Charcot-Leyden crystals. Fractional gastric analysis (Ewald test meal) at 15-minute intervals up to 105 minutes gave normal values for free hydrochloric acid and total acidity. Basal metabolic rate was +12.5 per cent. (Roth-Benedict apparatus — Aub-Du Bois standards.) Gastrointestinal fluoroscopy showed a normal esophagus, stomach and duodenum. The electrocardiogram showed sinus tachycardia. Temperature, 100° F.; pulse, 80; respiration, 22; blood pressure, 111 mm. of mercury systolic and 74 mm. of mercury diastolic; weight, 123 pounds.

Treatment and Course. Deep Roentgen ray radiation therapy was started 11 days after admission, that is, on November 2. The details of the dosage were as follows: Size of area, 9 by 12 cm.; milliamperes, 4; K-V, 200; filter, Cu. 0.5 mm.; Al., 1 mm.; distance, 30 cm.; per cent erythema, 25; time, 7 minutes. The blood picture (Table 1) showed a rapid reduction in the total white cell count in response to the 5 deep radiation treatments given between November 2 and December 10, 1928. The red cells were not adversely affected. It is interesting to note that during this period of treatment the percentage of reticulocytes was always slightly above normal.

Subjectively and objectively the response to deep radiation therapy was as striking and satisfactory as was the response hematologically. The outstanding feature of the clinical response, as was to be expected, was the strikingly rapid and complete reduction in the size of the spleen. Following the Roentgen ray therapy the patient experienced what might be regarded as postirradiation reaction, which manifested itself as nausea, "hot flashes," chilly sensations along the spine and profuse perspiration of the palms.

She was discharged to the return blood clinic on December 12, 1928. In Table 2 are given the dates of the return visits with the white cell counts and radiation treatments. During the first three visits to the return clinic, December 19 and 26, 1928, and January 9, 1929, the total white counts were 30,000, 26,400 and 11,400 respectively. Radiation therapy was given on the first two return visits and none on the third. The patient did not appear again at the return clinic for a period of about 9 months, that is, September 26, 1929, when her white count was found to be 130,200. The response to Roentgen ray therapy was quite rapid, as can be seen from

TABLE 2.—TOTAL WHITE CELL COUNTS AND DEEP RADIATION TREATMENTS WITH THEIR DATES, FROM DECEMBER 19, 1928, TO DECEMBER 19, 1929.

Date, 1928.	White blood cells.	Treatment.
Dec. 19	30,000	X P.S.
Dec. 26	26,400	X P.S.
1929.		
Jan. 9	11,400	None
Sept. 26	130,200	X A.S.
Sept. 30	86,700	X A.S.
Oct. 2	91,200	X A.S.
Oct. 7	72,900	X A.S.
Oct. 9	71,700	X P.S.
Oct. 14	50,600	X P.S.
Oct. 16	43,600	X P.S.
Oct. 24	29,600	None
Oct. 31	16,700	None
Nov. 21	5,100	None
Dec. 19	9,400	None

X A.S. = Deep radiation treatment over anterior spleen.

X P.S. = Deep radiation treatment over posterior spleen.

Details of radiation treatments are given under Treatment and Course in text.

TABLE 3.—TOTAL WHITE CELL COUNTS, DIFFERENTIAL FORMULAE, HEMOGLOBIN, RED CELL, COLOR INDEX AND RETICULOCTE DETERMINATIONS.
DEEP RADIATION TREATMENTS AND THEIR DATES, FROM JANUARY 16, 1930, TO MARCH 21, 1931.

Date.	Total white blood cells, thousands.	Myeloblasts.	Premyelocytes.	Myelocytes.	Metamyelocytes (I).	Metamyelocytes (II).	Neutrophils.	Lymphocytes.	Monocytes.	Eosinophils.	Basophils.	Plasma cells.	Radiation treatment.	Hemoglobin (Dare), per cent.	Grams.	Erythrocytes.	Color index.	Reticuloocytes, per cent.
1930.																		
Jan. 16 . . .	9.9	0	1	2	0	4	83	4	2	2	2	0	None	67.0	9.1	5.03	0.67	3.6
Feb. 13 . . .	12.4	None					
Mar. 13 . . .	14.6	None					
Mar. 18 . . .	15.7	None					
Apr. 15 . . .	23.8	None					
Apr. 23 . . .	21.5	0	3	5	2	10	67	5	2	3	2	1	None					
July 18 . . .	39.3	None					
July 30 . . .	46.6	None					
Sept. 12 . . .	66.4	None					
Sept. 18 . . .	70.3	1	8	6	14	14	47	3	4	1	2	0	None					
Oct. 21 . . .	78.6	None					
Nov. 19 . . .	100.4	A.S.					
Nov. 26 . . .	112.6	0	12	14	7	33	32	0	1	1	0	0	A.S.					
Dec. 5 . . .	80.6	A.S.					
Dec. 9 . . .	109.6	A.S.					
Dec. 12 . . .	103.8	P.S.					
Dec. 16 . . .	77.6	1	13	10	7	19	41	1	2	4	2	0	P.S.					
Dec. 19 . . .	80.0	P.S.					
Dec. 22 . . .	97.8	P.S.					
Dec. 29 . . .	36.5	None					
1931.																		
Jan. 16 . . .	15.0	None					
Feb. 19 . . .	9.0	None					
Mar. 3 . . .	13.0	None					
Mar. 21 . . .	15.2	0	0	8	1	2	77	6	3	1	1	1	None	94.6	16.0	5.05	0.94	2.0

X A.S. = Deep radiation treatment over anterior spleen.
 X P.S. = Deep radiation treatment over posterior spleen.

Table 2. If one compares the data in Tables 1 and 2 the following are apparent: that the number of treatments was not large; that the reduction in the total number of white cells was rapid; that the treatments were given only over the anterior and posterior spleen.

Pregnancy and Subsequent Course. The patient had her last menstrual period in December, 1929. In January, 1930, she missed her menstrual period and began to complain of symptoms that from previous experience she associated with pregnancy, as follows: anorexia, nausea and vomiting. In April, 1930, there were definite physical evidences of pregnancy. In May, because of persistent vaginal bleeding, she was admitted to the hospital, where a diagnosis of threatened abortion was made. With rest in bed and with the use of sedatives, the bleeding stopped and the patient was discharged at the end of a week. On September 13 the patient went into labor spontaneously and was delivered of a male child weighing 7 pounds 10 ounces. The labor was entirely uncomplicated and of comparatively short duration, less than 24 hours elapsing from the time of beginning premonitory symptoms until delivery. During the period of gestation the patient complained of anorexia, nausea, vomiting, feeling of fullness in the abdomen, especially in the left upper quadrant, the appearance of crops of purpura, especially over the lower extremities and transient attacks of numbness and tingling of the fingers and toes. Excepting the external manifestations of pregnancy, the patient's physical appearance was but little altered from that presented prior to the onset of pregnancy.

From an examination of Table 3 it can be seen that the total white count increased during the period of pregnancy to a level of about 70,000 at the time of delivery and the differential formulæ also changed in that there occurred an increase in the number of less differentiated granulocytic cells. The white count continued to rise after delivery, but here again a short course of deep radiation treatments over the anterior and posterior spleen was followed by a striking and prompt decrease in the total number of white cells. During the period extending from January 16, 1930, that is, the date of the onset of pregnancy, to March 21, 1931, the date of this writing, there have been no striking qualitative or quantitative variations in the red cell picture.

Comment. From a study of Tables 1, 2 and 3, it is quite evident after radiation that the total leukocyte count never reached a very high level. At no time during the course of the disease could any evidence be adduced from the clinical findings and from a study of the differential formulæ that a chronic form of the disease was becoming acute. The striking response of the white cells to deep radiation therapy is quite apparent and noteworthy. There were three series of deep radiation treatments of seven, seven and eight treatments respectively with results as previously given.

There is no evidence that the pregnancy aggravated the course of the leukemia in this patient. As far as can be determined the child is perfectly normal, hematologically and physically. In the course of the deep radiation therapy, no attempt was made to radiate the ovaries, the treatments being confined to the anterior and posterior spleen. Because of this fact, there does not seem to be any valid reason for this patient's not becoming pregnant if one excepts the existence of leukemia as preventing the occurrence of pregnancy.

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**THE INCIDENCE AND SITUATION OF MYOCARDIAL
INFARCTION IN ONE THOUSAND CONSECUTIVE
POSTMORTEM EXAMINATIONS.***

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CORONARY occlusion and myocardial infarction have been the subject of many clinical, electrocardiographic and pathologic studies in recent years. Communications dealing with the pathologic details have been relatively few and particularly lacking in details relative to the incidence and situation of infarction in a large series of cases.

Benson and Hunter found 200 cases of obstructive disease of the coronary arteries in 1750 postmortem examinations. However, they were able to demonstrate acute or chronic infarction in only 76 of these cases, an incidence of infarction of 4.3 per cent. In 54 additional subjects (3 per cent) fresh thrombi were present in the coronary arteries, without infarction or aneurysm having been produced. They did not give the details of the situation of the infarction. Parkinson and Bedford observed that the main branch of the left coronary artery was occluded in 3 cases, the anterior descending branch in 24, the circumflex branch in 10 and the right coronary artery in 18. They did not give the details of the situation of infarction in their cases. Other reports^{7,8,13} contain valuable observations on the pathology of coronary occlusion, but the authors did not pay particular attention to incidence and situation of infarction nor did they report the situation of the obstruction in the coronary arteries.

In undertaking any study of myocardial infarction, the normal or

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usual distribution of the coronary arteries must be known. The recent investigations of Whitten, with his celluloid corrosion methods of demonstrating the cardiac circulation, have given the necessary information. Utilization of these preparations has been made in Figs. 1, 2 and 3.

As previously has been pointed out by Parkinson and Bedford and by Barnes and Whitten, myocardial infarction is almost completely confined to the left ventricle. It has not been emphasized before, however, that infarction in the left ventricle is found chiefly in 3 situations due to the distribution of the 3 main arterial branches

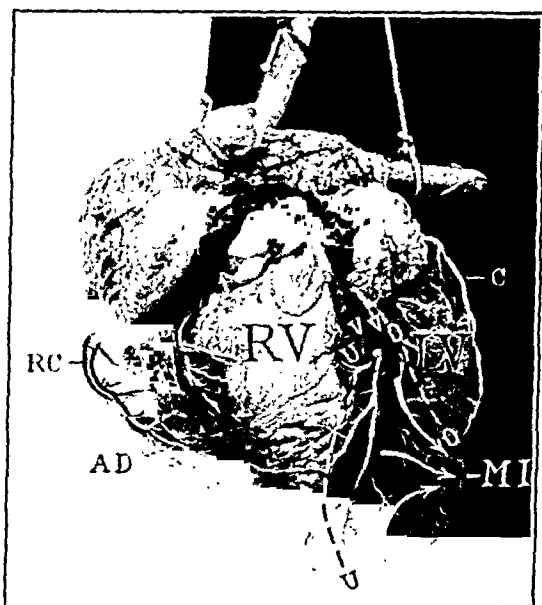


FIG. 1.—MI, Region partially or completely involved by myocardial infarction in 28 cases. In every instance the anterior descending branch of the left coronary artery supplied this portion of the heart. RV, right ventricle; LV, left ventricle; AD, anterior descending branch of the left coronary artery; C, circumflex branch of the left coronary artery; RC, right coronary artery; VV, veins. Region between U—U and O—O, roughly corresponds to the portion of the heart supplied by the anterior descending branch of the left coronary artery.

of the right and left coronary arteries responsible for its blood supply. Inasmuch as the several infarctions observed in this series conform more or less closely to 1 or more of these typical situations it is necessary to describe each in some detail.*

One type may be described as involving the apex and anterior portion of the left ventricle and is almost always due to occlusion of the anterior descending branch of the left coronary artery, or more rarely to occlusion of the main trunk of the left coronary vessel.

* For greater details regarding the types of infarction and their relation to blood supply the reader is referred to Whitten's observation,

The infarction usually occurs at considerable distance from the site of occlusion, so that the apex is almost invariably involved. With it a portion of the anterior $\frac{1}{3}$ to $\frac{1}{4}$ of the left ventricle is involved, extending upward a variable distance toward the base, rarely reaching a point more than $\frac{2}{3}$ to $\frac{3}{4}$ of the distance from the apex to the base. The adjacent interventricular septum is involved but the neighboring portion of the right ventricle almost always escapes serious injury. This will be referred to as the anterior apical type of infarction.

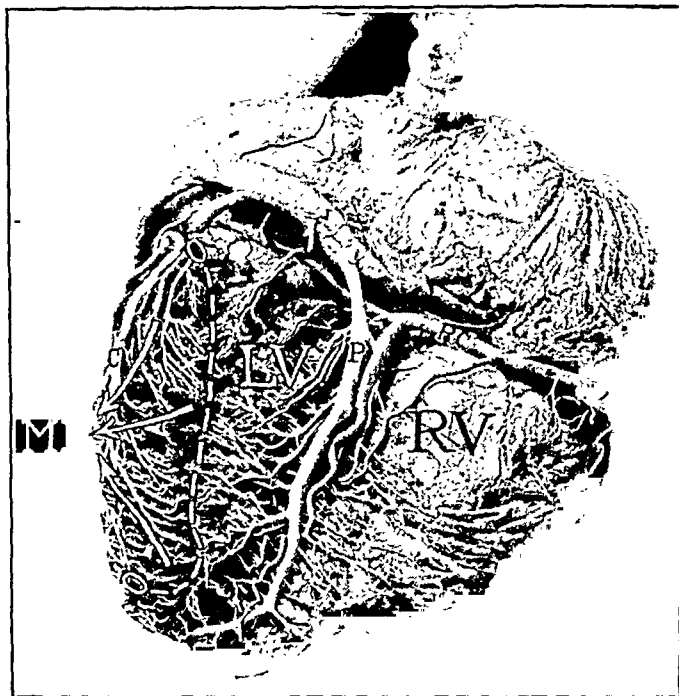


FIG. 2.—MI, Region partially or completely involved by myocardial infarction in 8 cases. In every instance the circumflex branch of the left coronary artery supplied this portion of the heart. RV, right ventricle; LV, left ventricle; P, posterior descending vein roughly marking the division between the right and left ventricles; RC, right coronary artery; C, circumflex branch of the left coronary artery; O—O, line roughly separating the portion of the left ventricle supplied by the circumflex branch of the left coronary artery from that supplied by the right coronary artery.

Infarction of the midventricle constitutes a second typical situation of infarction of the left ventricle. This infarction characteristically involves the obtuse margin of the left ventricle about midway between the base and apex, although it may occur at the base and occasionally well down toward the apex. This usually results from occlusion of the circumflex branch of the left coronary artery. The term midventricular infarct will be used when referring to an infarct in this situation in the left ventricle.

A third very common site of infarction in the left ventricle, and one that has been frequently overlooked, is the posterior basal

portion of the left ventricle. This usually involves the basal three-fifths of the posterior portion of the left ventricle, the adjacent portion of the interventricular septum, and very rarely a small border of the adjacent right ventricle. This usually results from occlusion of a branch or of the main trunk of the right coronary artery, although in an occasional case the circumflex branch of the left coronary artery is the site of occlusion. Variations of the region of infarction here depend on variations in blood supply, and occasionally the infarct at the posterior part of the base may

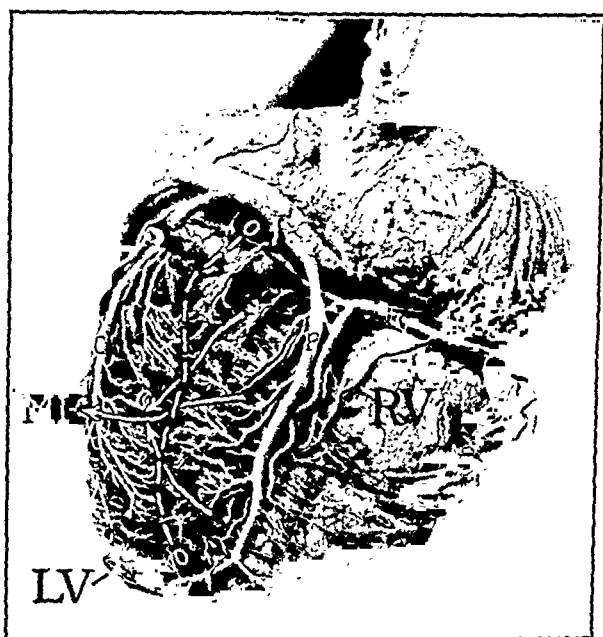


FIG. 3.—MI, Region partially or completely involved by myocardial infarction in 24 cases. This portion of the heart was supplied by the right coronary artery in 17 cases, by the circumflex branch of the left coronary artery in 5 cases, and by both the right coronary artery and the circumflex branch of the left coronary artery in 2 cases. RV, right ventricle; LV, left ventricle; RC, right coronary artery; P, posterior descending vein; C, circumflex branch of the left coronary artery; O—O, line roughly separating the portions of the left ventricle supplied by the circumflex branch of the left coronary artery from that supplied by the right coronary artery.

extend to the obtuse margin, to the apex, or to both. Infarctions in this portion of the left ventricle will be spoken of as posterior basal infarctions.

This study was undertaken to determine, as accurately as possible, the incidence and situation of infarction. The material was obtained from 1000 consecutive postmortem examinations performed at The Mayo Clinic. It included all ages and both sexes, and no cases were excluded on any ground.

In the 1000 consecutive postmortem examinations there were

49 hearts in which there was gross evidence of myocardial infarction, an incidence of 4.9 per cent. Forty of the subjects were men and 9 were women.

The infarctions described here were recognized by gross methods, either by inspection or palpation or both. The infarcts encountered were acute, healed acute, or chronic. Acute myocardial infarction has definite pathologic characteristics and needs no discussion. We have classified infarcts as healed acute when they were localized, when they led to more or less complete replacement of the ventricular wall by fibrous tissue, and whether or not there was an organized thrombus of the endocardium corresponding to the region of infarction. In a certain number of cases the designation of healed acute infarction was strengthened by a previous history indicative of acute coronary occlusion. When we use the term "chronic infarction" we have reference to those cases in which the fibrous replacement is less complete and more patchy in its distribution than that seen in healing following acute infarction, although at times it may be impossible to distinguish the two types. We believe that chronic infarction results from the gradual, almost complete obliteration of the lumen of a coronary vessel which supplies a region that is involved. Cases in which chronic infarction was localized are included in the statistics regarding situation of infarction. In an occasional instance, chronic infarction is diffuse, tends to exist in the form of subendocardial fibrosis and involves the entire left ventricle more or less completely. It is not unusual for acute or healed acute infarction to be present in a left ventricle which is the seat of diffuse fibrosis of the chronic type.

Of the 49 infarctions, 47 had occurred among patients who had died at 40 years of age or more, an incidence of 6.86 per cent. Approximately 70 per cent of the infarctions had occurred among patients who were between the ages of 50 and 69 years when they died. The distribution of cases and the incidence of infarction by decades of life is given in Table 1.

TABLE 1.—DISTRIBUTION OF CASES AND INCIDENCE OF INFARCTION BY DECADES OF LIFE.

Age groups.	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
Subjects examined (total 1000)	107	37	62	109	167	223	203	74	15	3
Infarction	0	1	0	1	6	18	17	5	0	1
Percentage of infarction	0.0	2.7	0.0	0.9	3.5	8.0	8.3	6.7	0.0	33.3

One patient had had a definite history of syphilis, and 1 a questionable history of it, but the Wassermann reaction of the blood of both had been negative. The Wassermann reaction of blood and

spinal fluid of 1 patient had been positive and there had been definite neurologic evidence of syphilis of the central nervous system.

The blood pressure of 42 patients had been recorded at the time of their admission. The systolic blood pressure of 8 patients had been more than 150 mm. of mercury and the diastolic pressure more than 100 mm. In 5 cases the systolic pressure had been less than 150 mm. and the diastolic more than 100 mm. In 18 cases the systolic pressure had been less than 150 mm. and the diastolic less than 100 mm.

Five patients had given histories of angina pectoris, or dyspnea, or both, preceding the history that was indicative of the first coronary occlusion. In 24 subjects with myocardial infarction there had been a definite history of coronary occlusion. Twelve of these patients had had multiple myocardial infarctions, 9 of whom had given histories of a second coronary occlusion.

As near as could be determined the myocardial infarction had been the cause of death in 18 cases, a contributing cause in 19 cases, a possible contributory cause in 7 cases, and in 5 cases it had played no appreciable part in causing death.

The electrocardiographic changes observed following coronary occlusion have been described.^{2,6,9,11} Electrocardiograms had been taken in 35 of the cases in the group described here. In 11 cases of acute infarction the electrocardiograms had been characteristic of the situation of infarction according to the criteria presented by Barnes and Whitten.³ In 19 cases of healed acute or chronic infarction electrocardiographic abnormalities that were not pathognomonic of infarction had been observed. These had included instances of significant *T* wave changes, bundle-branch block, auricular flutter, and auricular fibrillation. The lack of changes characteristic of infarction in this group is accounted for, in some cases, by the fact that the infarctions were ancient, and in some cases by the fact that the occurrence of bundle-branch block had obscured the electrocardiographic features that might have been indicative of myocardial infarction. The electrocardiograms of 5 patients had not revealed significant changes.

The weight of the hearts tended to exceed the average calculated weight for the sex and age of the patients. Seven hearts weighed between 300 and 400 gm.; 17, between 400 and 500 gm.; 12, between 500 and 600 gm.; 7, between 600 and 700 gm.; 5, between 700 and 800 gm., and 1 weighed 800 gm. It seems certain that any heart which weighs 500 gm. or more is hypertrophied and a little more than half of the hearts exceeded that weight. We look on this increased size of the heart as being a result of associated hypertension which has been shown to have been present in 24 of 42 patients in whose cases readings of blood pressure were obtained. On the other hand, coronary occlusion and myocardial infarction occurred in cases in which the hearts were of normal size and blood

pressure was normal. It must be emphasized therefore that neither hypertension nor cardiac hypertrophy is a necessary concomitant of coronary sclerosis or occlusion.

Acute or chronic disease of the pericardium related to myocardial infarction was observed in 11 of the 49 cases. This ratio, as indicative of the incidence of pericarditis in cases of myocardial infarction, may be a little too high; it was not always possible to be sure that a chronic adherent pericardium was a relic of acute pericarditis due to myocardial infarction.

Certain traditional conceptions as to the branches of the coronary arteries most prone to undergo acute occlusion and as to the predisposition of certain branches to develop coronary sclerosis have gained wide acceptance. The prevalent idea is that most acute occlusions occur in the anterior descending branch of the left coronary artery. This has led to the designation of this branch as "the artery of sudden death." Although it still exceeds other branches in the frequency of its acute occlusion, the preponderance of such an occurrence is not nearly so great as commonly has been supposed.

Table 2 shows that definite occlusion of the anterior descending branch of the left coronary artery was demonstrated in 18 cases; of the circumflex branch, in 7, and of the right coronary artery, or a branch, in 9. However, in those cases in which definite occlusion could not be found, the vessel or branch supplying the region of infarction was identified by careful dissection. Most of these vessels presented segments which were almost completely occluded, and in some organization and canalization of thrombi was apparent. A study of these vessels, which were identified by dissection, in relation to their distribution to the regions of infarction, shows that the anterior descending branch of the left coronary artery was responsible for cardiac infarction in 10 cases, the circumflex branch, in 10, and the right coronary artery, in 11. Combining the group in which arteries were definitely occluded with the group in which the offending artery was identified by dissection it is seen that the anterior descending branch of the left coronary artery was responsible for gross myocardial infarction in 28 instances, the circumflex branch, in 17, and the right coronary artery, in 20.

The greater apparent frequency with which thrombi are demonstrated in the anterior descending branch of the left coronary artery in comparison with the other branches which supply the left ventricle is probably due chiefly to circumstances. First, the anterior descending branch is studied more carefully by the average pathologist than is the circumflex branch and the right coronary artery. This is particularly true of the branches of the right coronary artery distributed to the left ventricle, for dissection of these branches is tedious and at times somewhat difficult. In the second place, longitudinal incision of the anterior descending branch without

TABLE 2.—SITUATION OF INFARCTION AND OCCLUSION.*

Case.	Situation of infarction in left ventricle.				Artery demonstrated to be occluded.			Artery to region of infarction when occlusion not demonstrated.		
	Anterior portion and apex.	Median ventricular portion	Posterior basal portion	Diffusely beneath endocardium	Left coronary.		Right coronary	Left coronary.		Right coronary
					Anterior descending branch	Circumflex branch		Anterior descending branch	Circumflex branch	
1	-	+	+	-	+	+	+	-	+	+
2	+	+	+	-	-	-	-	+	-	-
3	+	-	-	-	+	-	-	-	-	-
4	+	-	-	-	+	-	-	-	-	-
5	+	-	-	-	+	-	-	+	-	-
6	+	-	-	-	+	-	-	-	+	-
7	+	+	-	-	+	-	+	-	-	-
8	+	-	-	+	-	+	-	-	-	-
9	+	-	-	-	-	-	-	+	-	-
10	+	-	-	+	+	+	-	-	-	-
11	-	-	+	+	+	+	-	-	-	-
12	-	-	-	-	+	-	-	-	-	-
13	+	-	-	-	+	-	-	-	-	-
14	+	-	+	-	+	-	+	-	-	-
15	+	-	+	-	-	-	+	-	-	-
16	-	-	-	-	-	-	-	+	-	+
17	+	-	+	-	-	-	-	-	-	-
18	-	-	-	-	+	-	-	-	+	-
19	+	-	-	-	-	-	-	+	-	-
20	+	+	+	-	-	+	+	-	-	-
21	-	-	+	-	-	+	+	-	-	-
22	-	-	+	-	-	+	-	-	+	-
23	-	+	-	-	-	-	-	-	-	-
24	-	-	-	-	-	-	-	-	-	-
25	+	-	+	-	+	-	+	-	-	+
26	+	-	+	-	+	-	-	-	+	-
27	+	-	+	-	-	-	-	+	-	-
28	-	-	+	-	-	-	-	-	-	+
29	+	-	+	-	-	-	-	-	+	+
30	-	-	+	+	-	-	-	-	-	-
31	+	-	+	+	-	-	+	-	-	-
32	-	-	+	-	+	-	-	-	+	-
33	+	-	+	-	-	-	-	+	-	-
34	-	-	+	-	-	-	-	-	-	+
35	+	-	+	-	-	-	-	-	-	+
36	-	-	+	-	-	-	-	-	-	-
37	-	-	-	-	-	+	-	-	-	-
38	+	-	-	-	-	-	-	+	-	+
39	+	-	+	-	-	-	-	-	-	+
40	-	-	+	-	-	-	-	-	-	-
41	-	-	+	-	-	-	+	+	-	-
42	-	+	+	-	-	-	-	-	+	-
43	-	-	-	-	-	-	-	-	-	-
44	-	+	+	-	-	+	+	-	-	+
45	+	-	+	-	-	-	-	+	-	+
46	-	+	-	+	-	-	-	-	+	-
47	+	-	+	+	-	+	-	-	-	-
48	+	-	-	-	-	+	-	-	-	-
49	+	-	-	-	-	-	-	-	-	-
Total	28	8	24	3	18	7	9	10	10	11

* The sign + is equivalent to the word "yes"; the sign -, to the word "no" under each heading.

dislodging a thrombus is certainly technically easier than similar incision of the arclike and at times tortuous right coronary artery. More lively suspicion that there may be thrombi occluding the right coronary artery and the circumflex branch of the left coronary artery and more painstaking study of those vessels will increase greatly the frequency of discovery of thrombi occluding those vessels.

As a corollary to the erroneous idea that the anterior descending branch of the left coronary artery is the usual site of coronary occlusion is the conception that most myocardial infarction is found in the apex and adjacent anterior portion of the left ventricle and anterior interventricular septum. Our investigation shows that gross myocardial infarction is found practically as commonly in the posterior basal portion of the left ventricle as in the apex and anterior portion (Table 2; Figs. 1, 2 and 3).

An attempt was made to grade on a scale of 1 to 4 the degree of sclerosis present in the right and left coronary arteries. We were under the impression that coronary sclerosis on the average was much more pronounced in the left coronary artery as compared with the right coronary artery. Our observations gave very little support to that idea. In 36 cases the degree of coronary sclerosis was estimated to be the same in the right and left coronary arteries. In 7 cases the sclerosis present in the left coronary artery was estimated to exceed that in the right by 1 point on our scale, in 3 cases, by 2 points, and in 1 case, by 3 points. In 2 instances the sclerosis of the right coronary artery was estimated to be greater than that in the left.

Furthermore, the frequency with which gross myocardial infarction occurs in the distribution of the right and left coronary arteries is probably a good index of the degree of sclerosis existent in those vessels. If we compare the number of infarctions observed in the region supplied by the right coronary artery with that observed in the region supplied by the anterior descending branch of the left coronary artery (Table 2) we do not find a great discrepancy.

Comment. It has become increasingly apparent that coronary thrombosis with myocardial infarction is a common occurrence in the human heart. The fact that in 6.8 per cent of subjects more than 40 years of age examined in a series of 1000 consecutive postmortem examinations, gross more or less localized infarction was found and that in 9 subjects 2 or more distinct infarctions were found, gives a conception of the incidence of this lesion. Seventy per cent of the cardiac infarctions were found among patients between the ages of 50 and 69 years.

This study serves to correct the impression that an overwhelming majority of cardiac infarctions occurs as results of occlusion of the anterior descending branch of the left coronary artery. It is no longer justifiable to designate the anterior descending branch as "the artery of coronary occlusion."

Furthermore, localized infarction is to be observed practically as frequently in the posterior basal portion of the left ventricle as it is in the apex and adjacent anterior portion of the left ventricle. It is important to point out that infarction in the posterior basal portion of the left ventricle often will be overlooked by the pathologist unless an incision through the left ventricle is made parallel with, and closely adjacent to, the posterior interventricular septum, extending from the apex to the mitral ring.

Barnes and Whitten described electrocardiographic changes by means of which it was possible to predict whether myocardial infarction would be found at necropsy to have involved the apex and anterior portion or the posterior basal portion of the left ventricle. The types of electrocardiographic changes characteristic of infarction in one and in the other of these regions were observed with equal frequency by Parkinson and Bedford. They felt that this equal frequency of occurrence of the 2 types were out of keeping with their observation that occlusion of the left coronary artery was twice as common as was occlusion of the right coronary artery. However, the circumflex branch of the left coronary artery fairly commonly supplies the posterior basal portion of the left ventricle. As a result of this fact, infarction in the posterior basal portion of the left ventricle may result from occlusion of the circumflex branch of the left coronary artery as well as from occlusion of the right coronary artery. Our study shows that cardiac infarction occurs in the posterior basal portion and in the anterior and apical portion of the left ventricle with approximately equal frequency. Thus Parkinson and Bedford's observation of the equal incidence of electrocardiographic changes pointing to infarction in the anterior and apical portion of the left ventricle on the one hand and pointing to infarction of its posterior basal portion on the other, is in harmony with our observations and supports rather than detracts from the localizing value of the electrocardiographic changes described by Barnes and Whitten.

Summary. In 1000 unselected consecutive postmortem examinations more or less localized myocardial infarction was recognized grossly in 49 subjects (4.9 per cent).

Of 685 of these subjects, 40 years of age or more, myocardial infarction was observed in 47 (6.86 per cent).

A majority of the subjects who had sustained myocardial infarction had had associated hypertension, as judged by the cardiac weights and the records of blood pressure.

Notable preponderance of arteriosclerosis in the left coronary artery over that found in the right was not observed in the hearts in which evidence of infarction was found.

Gross myocardial infarction resulting from coronary occlusion was practically confined to the left ventricle.

Myocardial infarction was observed in the posterior basal portion

of the left ventricle in 24 instances as compared with 28 instances in which it involved the apex and anterior portion. More careful pathologic study of the posterior basal portion of the left ventricle is urged in order that infarctions in that region be not overlooked.

In 28 instances infarction occurred in the region supplied by the anterior descending branch of the left coronary artery, as compared with 20 instances in which it occurred in the region of the left ventricle supplied by the right coronary artery. The designation of the anterior descending branch of the left coronary artery as "the artery of coronary occlusion" is no longer justifiable.

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STUDIES IN COMPLETE HEART BLOCK: II. A CLINICAL ANALYSIS OF 43 CASES.

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THE discovery of complete auriculoventricular heart block is ordinarily considered of serious significance to the individual in whom it is found, even though he shows no symptoms or signs of heart failure. Textbook descriptions of the condition emphasize

its gravity and usually state that sudden death is not infrequent. Recently, however, it has come to be recognized that heart block may occasionally exist for many years without seriously affecting the health of the subject. Thus, Lewis¹ states that heart block *per se* does not kill and that although it is usually a sign of serious and often progressive myocardial damage, it may exist for some time, especially in young individuals who are relatively and absolutely in good health. Sprague and White² also comment that in young people high-grade heart block may not be serious prognostically, and Harris³ in reporting a case of 28 years' duration stresses the fact that total block is compatible with normal life and that the prognosis depends on the degree of myocardial involvement. In a recent communication by Ellis and Weiss⁴ a study of the effect of heart block on the circulation as a whole was reported and an explanation given of the mechanism by which the organism adjusts itself to the altered circulatory conditions. The purpose of the present investigation was to gain further information regarding the factors which govern the occurrence of symptoms and which determine the prognosis as to life from an analysis of a series of cases of complete heart block.

Incidence. The present series includes all of the cases, proven by electrocardiogram, admitted to the Boston City Hospital from 1920 to 1931. There are 40 of these; and during this period a total number of 7515 electrocardiograms were taken. The total number of cases is brought to 43 by the addition of 3 cases from the Children's Hospital, Boston. These 3 represent the only proven cases observed at that hospital during the past 10 years, although electrocardiographic tracings have been taken there only during the past year, a total of 151 tracings having been made. Thirty-five of the 43 patients have been followed to the present time or until death. Twenty-nine showed persistent complete block while under observation, in 3 the block was intermittent, and in the remaining 11 it was temporary.

The patients ranged in age from 9 weeks to 78 years (Table 1). In general, the cases can be divided into two main groups, those below and those above 40 years of age. Seventy per cent of the cases occurred in the latter division. When the deaths in these age groups are considered, the increased mortality in the older persons is strikingly evident. All of the 10 persons below 40 years of age who have been followed are living; only 5 of the 25 who were 40 years of age or older are still alive. This marked difference in death rate is chiefly explained by the change with advancing age in the etiologic causes of the heart block, as will be demonstrated below.

Thirty of the patients were male and 13 female, a ratio of somewhat over 2 to 1. This predominance of heart block in males has been noted before.^{1,5,6}

TABLE 1.—AGE AND SEX DISTRIBUTION OF PATIENTS WITH COMPLETE HEART BLOCK AND MORTALITY IN VARIOUS AGE GROUPS.

Age, years.	No. of male patients.	No. of female patients.	Total patients.	No. of patients followed.	No. of followed patients living.	Followed patients living, per cent.
0 to 9	2	0	2	2	2	100
10 to 19	1	0	1	1	1	100
20 to 29	3	1	4	4	4	100
30 to 39	5	1	6	3	3	100
40 to 49	0	1	1	1	0	0
50 to 59	6	4	10	8	2	25
60 to 69	3	6	9	7	2	29
70 to 79	10	0	10	9	1	11
Total	30	13	43	35	15	43

Etiology (Table 2). The chief causes of total block are congenital defects, trauma, acute infections, intoxications as from digitalis, rheumatic fever, syphilis, arteriosclerosis and tumor. It is frequently impossible to determine with exactness clinically the etiology of complete heart block. This is especially true in young patients with no other evidence of cardiac disease. In a certain number of these individuals the heart block may be of congenital origin, in others it may have its inception during the course of some acute infection.

TABLE 2.—ETIOLOGICAL DISTRIBUTION OF PATIENTS WITH HEART BLOCK, WITH ITS RELATION TO AGE AND MORTALITY.

Etiology.	No. of patients.	Per cent of total patients.	No. of patients followed.	No. of followed patients living.	Per cent followed patients living.	Age limits of patients, years.	Average age of patients, years.
Permanent heart block:							
Congenital or unknown	9	31	7	7	100	<1-36	21
Diphtheria	1	3	1	1	100	27	27
Rheumatic fever	2	6	2	1	50	52-57	55
Arteriosclerosis	15	52	12	3	25	54-78	63
Arteriosclerosis and syphilis	1	3	0	54	54
Myxedema and syphilis	1	3	1	0	0	70	70
Total	29	..	23	12	52	<1-78	49
Intermittent or temporary heart block:							
Digitalis	8	57	7	2	29	21-73	58
Arteriosclerosis	4	28	4	0	0	49-76	62
Infection	2	14	1	1	100	29-53	41
Total	14	..	12	3	25	21-76	57

In the present series, of the 29 patients who showed a persistent block, there were 2 instances which were apparently of definite congenital origin, one in a child 9 weeks of age, and the other in a boy 9 years of age who had been known to have had a slow pulse rate since birth. Both had enlarged hearts with signs suggestive of congenital defects.* In 7 persons, all under 40 years of age, the etiology was undetermined, but the block was probably of congenital origin or followed some acute infection. Diphtheria was the probable cause in 1 person. This was the case of a young woman now 28 years of age in whom the sudden onset of a slow heart rate was observed during the course of a severe attack of diphtheria 24 years ago. This block has persisted to date, without giving rise to any disability or signs of cardiovascular disease. The rarity of persistent complete heart block with survival occurring during diphtheria has been previously noted.⁷ In only 4 of all the cases here reported was any definite history of diphtheria obtainable. This is in contrast to the observations of Butler and Levine⁸ who report that a history of diphtheria is more frequent in patients subsequently developing heart block than in a control series.

Two patients had a rheumatic cause. In 15 patients, 52 per cent of all of the cases of permanent heart block, arteriosclerotic changes were the probable cause of the block. Although syphilis is commonly considered one of the important etiologic causes of this condition, the blood Wassermann reaction was positive in only 2 of the 43 cases and both had an additional etiologic background, 1 of arteriosclerosis and the other of arteriosclerosis and myxedema, which very likely were primarily responsible for the lesion.

There were 3 patients, all with arteriosclerosis, with an intermittent complete block. Of the 11 cases of temporary auriculo-ventricular dissociation, 8 were apparently due primarily to digitalis. In 1 patient the only discernible cause was arteriosclerosis, and in the remaining 2 the temporary block occurred during the course of acute infections, 1 of acute rheumatic pancarditis and the other of septic sore throat.

Duration of Symptoms and Prognosis. The following analysis is confined to the 35 patients who were followed until the present time or death. Twenty-three of these showed a permanent block, and 12 had transitory A-V dissociation.

(A) *Permanent Heart Block.* The 7 patients with either a congenital or undetermined etiology for their heart block were all under 40 years of age and are all living. Four have no symptoms whatsoever in spite of leading active lives and 3 have only mild symptoms. In 2 of these persons there is good evidence that the block has existed for at least 9 years, and in a third it is known to have been present for over 7 years.

*. These 2 cases and 1 other will be reported in detail from the Children's Hospital.

The patient with block of diphtheritic origin of 24 years' duration is living and without symptoms.

Of the 2 patients in whom rheumatic infection was the etiologic agent, 1 had been a chronic cardiac invalid for years and died 30 months after the discovery of the block. The other is living but has experienced repeated severe attacks of congestive heart failure.

Three of the 12 individuals with arteriosclerotic heart block are living, and all of them have cardiac symptoms of slight to moderate extent. In the remaining 9 the duration of life after the discovery of the heart block was as follows: 1 lived five years with frequent Adams-Stokes attacks; 1 lived 3 years with increasing cardiac symptoms; 4 lived 2 to five months; and the remaining 3 died in less than 2 weeks.

The patient with heart block probably due to myxedema, arteriosclerosis and syphilis died suddenly of undetermined cause after having been observed for 5 years, during which time he experienced continually moderate symptoms of weakness and dyspnea.

One of the 12 living patients, a woman 68 years of age, has had infrequent Adams-Stokes attacks for the past 7 years. Seven of the 11 individuals who died were subject to such attacks of varying degrees of frequency and severity.

The lowest pulse rate in the patients with permanent block was 23, the highest 65 per minute. The majority fell between 30 and 50. No relationship was found between the pulse rate and the symptoms or mortality.

(B) *Temporary Heart Block.* Twelve patients with temporary or intermittent complete heart block have been followed. In 7 of these the etiologic agent appeared to be primarily digitalis intoxication, and all developed a normal rhythm within a few days after the digitalis was omitted. Two are living 2 and 5 years respectively after the occurrence of the heart block, 1 died of carcinoma about a year after the block, and 4 died of heart failure in from a few weeks to 18 months following the block. Two of the latter had complicating factors in the causation of the block; one, coronary thrombosis and the other, subacute bacterial endocarditis.

The patient who developed a complete block of short duration during the course of septic sore throat is now living and well 5 years later. The 4 persons with an arteriosclerotic background all died after pronounced cardiac symptoms had existed for 2, 3, 6 and 7 months respectively. Three of these individuals had varying degrees of block during the greater part of the time they had symptoms, although complete block existed in each for relatively short periods.

Three of the 4 persons dying with arteriosclerotic heart block had repeated Adams-Stokes seizures. None of the other patients subsequently dying developed such attacks. Of the living patients, the one whose block occurred during septic sore throat had several

attacks while the block persisted but none since. None of the other living patients showed this symptom.

The ventricular rates in the group showing temporary heart block varied from 33 to 100 per minute, all but 3 falling between 33 and 50. No correlation was found between the cardiac rate and the etiology, course or outcome.

Cardiac Enlargement. Only 7 of the 43 cases analyzed showed no cardiac enlargement. In these 7 patients the blood pressures were normal. Six of the 35 cases followed showed no enlargement; 5 of these are still living and have a diverse etiology. It is thus apparent that although cardiac enlargement in heart block may exist in persons in a relatively good state of health, it is unusual for the hearts of patients with this condition to be of normal size in the presence of marked myocardial damage, particularly if the blood pressure is elevated.

Electrocardiographic Findings. Five of the 43 patients had auricular fibrillation with complete block. An analysis of the electrocardiographic tracings in the 35 patients who were followed is given in Table 3. The greater frequency of abnormalities usually

TABLE 3.—ELECTROCARDIOGRAPHIC ABNORMALITIES ACCOMPANYING COMPLETE HEART BLOCK.

	Type of heart block.				Total.
	Permanent.		Temporary.		
	Alive.	Dead,	Alive.	Dead.	
Total patients followed	12	11	3	9	35
No abnormality*	7	3	2	4	16
Auricular fibrillation	1	2	0	1	4
Intraventricular block	1	2	0	2	5
Bundle-branch block	0	2	1	0	3
Inverted or diphasic T_1 or T_2	3	2	0	2	7
Patients with no abnormality, per cent*	58	27	67	44	46

* Not including the heart block or axis deviation.

considered indicative of cardiac damage among the patients that died is evident. In many instances the electrocardiograms were taken months and even years before the death of the patients so that the abnormalities encountered do not necessarily represent terminal electrocardiographic changes.

Six of the 43 patients showed an irregularity in the spacing of the P - P intervals commented upon by Wilson and Robinson.⁹ When a ventricular complex fell between the P waves the P - P interval was distinctly shorter than when no ventricular complex intervened. Two of these persons are known to be living and symptomless with heart block of congenital and diphtheritic etiology respectively, 1 had temporary block of arteriosclerotic origin and is dead, and 3 have not been followed. The etiology in 1 of these 3 cases was arteriosclerosis and in 2 undetermined.

Twenty-two patients showed left axis deviation, 1 right axis

deviation, 4 bundle-branch block, and 16 normal axis. No correlation was found between the axis and the etiology, functional condition, or mortality.

Arterial Blood Pressure. It is commonly held that in complete heart block there is characteristically an increased systolic and a normal diastolic pressure, resulting in a distinct and often very marked widening of the pulse pressure. So far as the diastolic pressure is concerned the findings in this series support such a belief. In only 3 of the 43 cases was the diastolic pressure 100 mm. of mercury or over. In the great majority of patients it fell between

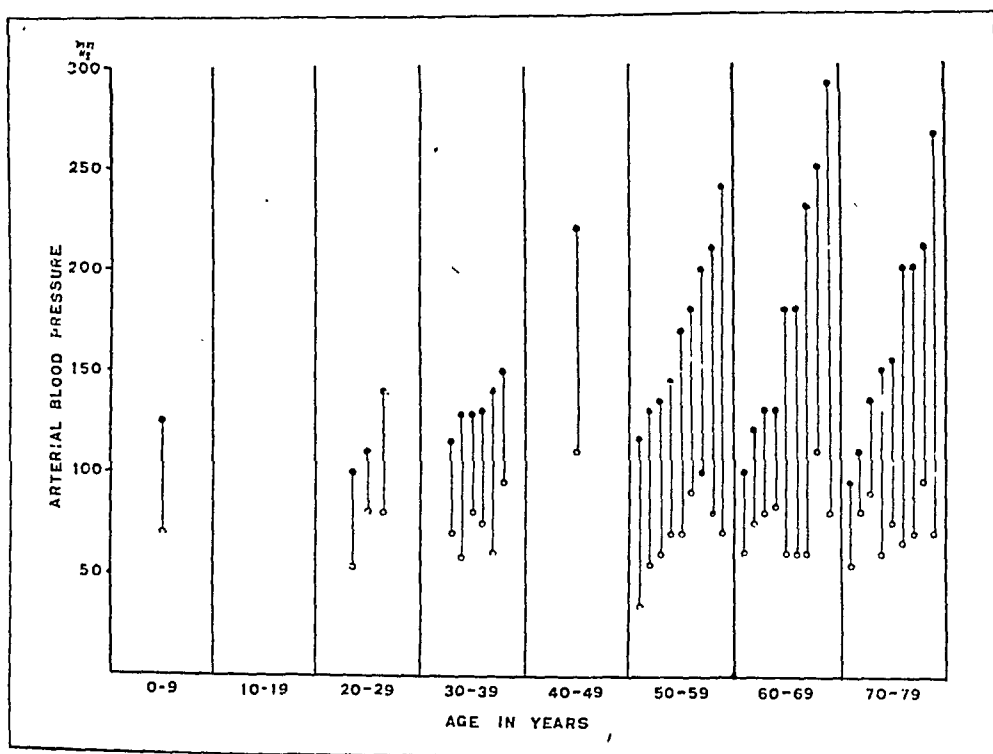


CHART I.—Arterial blood pressure in various age groups of patients with complete heart block. Solid circles represent the systolic, and hollow circles the diastolic pressures.

60 and 80 mm. of mercury. A markedly increased pulse pressure, *i.e.*, a systolic hypertension, was found to occur, however, only in the older age groups (Table 4, Chart I). This corroborates results previously reported by Ellis and Weiss⁴ which indicate that in complete heart block a definitely widened pulse pressure occurs usually only when the peripheral vascular system is sclerosed. The converse finding, that of low systolic and relatively low pulse pressures in patients with arteriosclerosis, observed in a few cases of the present series, is probably caused, in part at least, by failing cardiac function.

TABLE 4.—ARTERIAL BLOOD PRESSURES AND PULSE PRESSURES IN VARIOUS AGE GROUPS.

Age.	No. of patients.	Average arterial blood pressure.		Range of pulse pressure, mm. Hg.	Average pulse pressure, mm. Hg.
		Systolic, mm. Hg.	Diastolic, mm. Hg.		
0 to 9	2	125	70	55	55
10 to 19	1				
20 to 29	4	116	71	30-60	45
30 to 39	6	131	73	45-80	60
40 to 49	1	220	110	110	110
50 to 59	10	163	69	75-170	101
60 to 69	9	190	74	50-210	107
70 to 79	10	169	73	40-195	95

The effect of age and the state of the peripheral vascular system on the pulse pressure is illustrated more strikingly if groups are compared in which the possible influence of myocardial failure on the blood pressure has been eliminated. In Table 5 this is done. The first group is of young persons with no evident arteriosclerosis or myocardial damage other than the heart block. The second group comprises persons 50 years of age or older with varying degrees of arteriosclerosis but with very slight or no cardiac symptoms. The difference in pulse pressures is immediately apparent. None of the young persons had pulse pressures in excess of 60; only 2 of the old patients showed pulse pressures below 70.

TABLE 5.—COMPARISON OF ARTERIAL BLOOD PRESSURES IN PATIENTS WITH AND WITHOUT ARTERIOSCLEROSIS.

Patients with no evidence of myocardial damage or arteriosclerosis.					Patients with evidence of arteriosclerosis but having no or slight symptoms.				
Patient.	Age.	Arterial blood pressure, mm. Hg.		Pulse pressure, mm. Hg.	Patient.	Age.	Arterial blood pressure, mm. Hg.		Pulse pressure, mm. Hg.
		Sys-tolic.	Dias-tolic.				Sys-tolic.	Dias-tolic.	
1	33	128	80	48	8	60	132	80	52
2	33	115	70	45	9	68	290	80	210
3	29	110	80	30	10	70	150	60	90
4	21	100	55	45	11	70	135	88	47
5	36	150	95	55	12	50	200	100	100
6	9	125	70	55	13	65	250	110	140
7	28	140	80	60	14	53	116	34	82
					15	58	145	70	75
					16	78	265	70	215
					17	58	240	70	170

If the blood pressures are analyzed according to etiology, the only correlation is that the causes which tend to affect the older age groups are accompanied by higher pulse pressures.

No correlation was found between the pulse rate and blood pressures.

In the instances in which blood pressures were recorded in persons both during complete heart block and when normal rhythm had been restored there was no constant tendency for the systolic or diastolic pressures to change in any given direction.

Discussion. The present series is too small to permit of significant statistical analysis. Certain definite facts appear, however, and from them conclusions may be drawn. Complete heart block *per se* does not necessarily jeopardize the health or life of the individual having it. This is particularly evident from a consideration of 4 of the relatively young persons in this series in 2 of whom the block is known to have existed for 24 and 7 years respectively, and in the other 2 to have been present almost certainly for 9 years, without objective or subjective evidence of cardiac deterioration or failure.

Dr. Paul D. White has kindly given me permission to mention here 2 of his cases of complete heart block. These are both in women; one is aged 41 years and the other is about 35 years old. They have been known to have had persistent heart block for at least 14 and 15 years respectively. Both have been followed clinically and checked by electrocardiogram during this time. In neither was the etiology determined. Both are quite well and lead active lives, 1 being an ardent and excellent golfer. Instances have been reported in the literature of total heart block existing in persons in good health for many years, notably the case reported by Harris³ of 28 years' duration, and that by Willius⁶ lasting 15 years.

Heart block should not, therefore, be considered a disease entity either from the etiologic or prognostic viewpoint. It should rather be considered merely as a sign of cardiac abnormality which is usually indicative of severe cardiac damage. The regulation of the life and the prognosis given an individual depend on a consideration of other aspects of his condition. These are: (1) The underlying etiology. When the block is due to arteriosclerosis it is usually indicative of widespread cardiac damage, whereas if the etiology is of congenital or undeterminable origin, the block is more likely to be caused by a localized lesion or defect in the conducting system and the myocardium may be unimpaired; (2) with increasing age the prognosis becomes worse, probably due to a shift in the predominating etiologic causes with advancing age; (3) Adams-Stokes attacks usually are of grave import, indicating as they do periodic circulatory insufficiency, ordinarily due to a breakdown in the conducting and exciting mechanism of the heart; (4) any of the electrocardiographic changes usually considered an indication of cardiac damage are evidence of poor cardiac function; (5) a normally-sized heart in a patient with total block indicates an adequately functioning myocardium and carries a better prognosis. From no one of these factors alone should a prognostic conclusion be drawn,

but from an evaluation of all of these aspects a decision can be reached as to the significance of the lesion and the probable future progress of the condition.

In the previous study of heart block reported by Ellis and Weiss a picture of the functioning and adjustments of the circulation as a whole was presented. The present clinical study supports the previous findings, in particular regarding the arterial blood pressure in heart block. The systolic hypertension and increased pulse pressure frequently observed in complete heart block have been considered an index of the increased ventricular discharge by most observers. While undoubtedly there is an increased cardiac stroke output in this condition, this usually occasions a greatly increased pulse pressure only when the peripheral arterial system is so rigid, through sclerotic changes, that a high initial systolic pressure becomes essential to maintain the forward movement of the blood during the prolonged diastolic pauses. In young persons, without arteriosclerosis, the elastic vessels can stretch to accommodate the increased mass of blood projected into them with each beat, and by contracting aid in its forward propulsion without the necessity for a raised systolic pressure. Such young individuals are spared, therefore, the added strain which hypertension in itself imposes on the heart and circulation. All of the patients of this series who were relatively young and without evidence of peripheral sclerosis had arterial blood pressures which did not differ strikingly from the normal.

Summary. 1. An analysis is presented of 43 cases of complete auriculoventricular block in patients ranging in age from 9 weeks to 78 years. Seventy per cent of the patients were over 40 years of age and the same percentage were malés. In 29 cases the block was permanent, while in the remainder it was intermittent or temporary.

2. Fifty-two per cent of the cases of permanent block were due to arteriosclerosis, 31 per cent were of undetermined origin, but in most of these instances were probably either congenital or dependent upon an acute infection. Diphtheria, syphilis and rheumatic infection were responsible for a small number of cases. Digitalis was the chief etiologic agent producing transitory block, although arteriosclerosis and infections caused a lesser proportion.

3. Complete heart block *per se* may exist for very prolonged periods of time without damaging the health of the patient. Four cases are recorded in which the block is known to have existed for 24, 15, 14 and 7 years respectively, and 2 more in which it has almost certainly lasted 9 years. The chief factors governing the prognosis appear to be etiology, age, Adams-Stokes seizures, electrocardiographic abnormalities, and cardiac size.

4. A discussion of the significance of arterial blood pressure findings is presented. Young persons with complete heart block

may have essentially normal blood pressures. A systolic arterial hypertension and wide pulse pressure usually occur in heart block in persons giving evidence of peripheral arteriosclerosis.

NOTE.—It is a pleasure to acknowledge my appreciation to Dr. Kenneth D. Blackfan of the Children's Hospital, Boston, for permission to report the cases from that hospital, and to Miss Mildred Adell for assistance in following the patients.

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THE COLONIC ADMINISTRATION OF OXYGEN IN EXPERIMENTAL ANOXEMIA.

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THE 4 experiments to be reported in this paper were undertaken to determine whether within a given period of time a sufficient amount of oxygen would be absorbed from the colon of a dog to relieve or abolish a degree of experimental anoxemia comparable to that which is sometimes seen clinically in human disease. Such a study seemed capable of yielding knowledge of practical importance when we recalled the following known facts:

1. The value of oxygen as a therapeutic measure. At the present time its use is widespread and those who have had most experience

with it are uniformly agreed as to its value as a therapeutic agent. Its ability to raise the oxygen content and per cent oxygen saturation of the arterial blood in most cases of acute pneumonia with anoxemia was clearly demonstrated by a study of the blood gases in 137 cases of pneumonia at the Hospital of the Rockefeller Institute before and after exposure to a 40 per cent oxygen concentration in a specially made chamber (Binger¹).

2. Its inability, when given by inhalation, to abolish or relieve anoxemia in the occasional case of pneumonia with extensive pulmonary involvement and "wet" lungs.

3. The relative scarcity and limited accommodations of oxygen chambers, even though it is uniformly conceded that the chamber is the most efficient and most convenient means of giving oxygen and by far the most pleasant for the patient.

4. The inaccessibility of oxygen tents which are recommended as the second best means of giving oxygen; and the inconvenience and noise which are associated with their use.

5. The discomfort and limited effectiveness of the administration of oxygen by means of nasal catheters or face masks.

6. The fact that the absorption of oxygen from the gastrointestinal tract has been demonstrated experimentally.

When these facts were considered it occurred to us that the effective and harmless administration of oxygen by some route other than the lungs would not only be of interest but under certain clinical conditions was actually indicated. We knew that this idea had occurred to others, but found no reports in the literature, either experimental or clinical, of the absorption of oxygen through the colon at a sufficient rate to raise the per cent oxygen saturation of the arterial blood in anoxemia.

Kato² studied the changes in various gases which he introduced into isolated sections of the small intestine of anesthetized rabbits and found that carbon dioxid disappeared rapidly, oxygen slowly and hydrogen and nitrogen not at all. He noted further that small amounts of carbon dioxid and nitrogen appeared in the intestinal lumen after the injection of hydrogen and nitrogen and caused an increase in the original volume. Schoen³ made similar studies on dogs, including the large intestine, and in general noted the same results. These studies by Kato and Schoen and more recent studies by McIver, Redfield and Benedict⁴ and others indicate that there is an interchange of gases between the lumen of the gastrointestinal tract and the circulating blood, which resembles the gaseous interchange in the lungs and which, like it, is governed by the physical laws of diffusion.

The slow absorption of oxygen was not encouraging for the study which we had planned. Nevertheless, it must be borne in mind that the observations alluded to were made on animals whose blood, presumably, was normally saturated with oxygen. Assuming an

adequate supply of oxygen through the colon, the tendency for it to be absorbed would be greater when the oxygen tension of the blood is low and there is consequently a greater difference between the partial pressure of the gas within and without the lumen of the gut. Such were the conditions in our experiments. Our results, however, were disappointing in that they were negative and whatever importance can be attached to them would seem to lie in the field of academic rather than of practical interest.

Method. Dogs were used. Each animal received 2 colonic irrigations with warm suds, 1 on the day preceding and the other on the morning of the experiment. Several hours after the second irrigation the animal was anesthetized by the intravenous injection of barbital sodium (0.3 gram

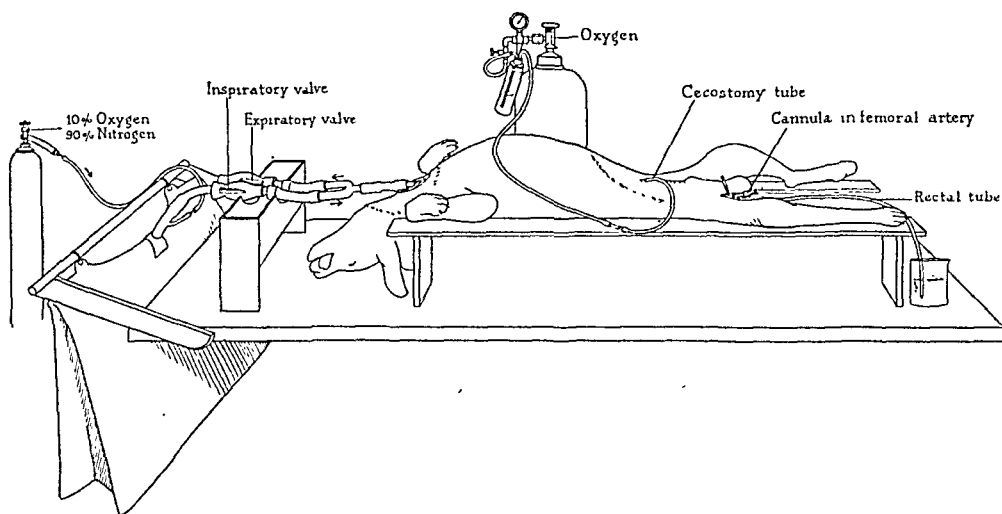


FIG. 1.—Diagrammatic view of the apparatus which was used in Experiments 3 and 4. In Experiments 1 and 2 oxygen was administered through the rectal tube and the cecostomy was not necessary. Otherwise the preparation used in these two experiments was identical with the one shown in the diagram.

per kg. body weight). The trachea was isolated through a midline incision, opened horizontally, and a glass cannula tied snugly in position. A second cannula was then inserted into one femoral artery for the withdrawal of blood samples. At the end of a control period, during which the animal breathed room air, the first blood samples were taken. Immediately after this the tracheal cannula was connected through a system of inspiratory and expiratory valves with a Douglas bag containing a gas mixture of 90 per cent nitrogen and 10 per cent oxygen (Fig. 1). By causing the animal to inspire from the bag and expire into room air, the oxygen percentage of the inspired air was maintained at a constant low level. In this way the oxygen tension of the alveolar air was reduced to such a degree that anoxemia regularly resulted. After the animal had breathed this oxygen-poor mixture for a given period of time (varying from 12 to 19 minutes) second blood samples were withdrawn in order to determine the degree of anoxemia which resulted. The administration of oxygen was then begun. In the first experiment (No. 1) 3000 cc. of oxygen were introduced through a rectal tube during a period of 15 minutes. In the second (No. 2) 5500 cc. were given during a period of 61 minutes. In the third and fourth experiments

the oxygen was introduced at a given rate through a small rubber catheter which previously had been fixed in the cecum and allowed to pass through the colon and out through a rectal catheter, the end of which was immersed in water. In these two experiments oxygen was administered for periods of 20 and 30 minutes respectively. The third blood sample was then taken, the administration of oxygen discontinued and the animal again allowed to breathe room air. From 6 to 19 minutes later a final sample of blood was withdrawn. At frequent intervals during the progress of each experiment the pulse and respiratory rates were counted with the aid of a stopwatch.

The oxygen content of the blood samples was estimated by the manometric method of Van Slyke and Neill² and the results expressed in volumes per cent. The oxygen capacity of each sample was estimated after rotating the blood for 5 minutes in a flask in which it was exposed to room air. The percentage saturation of the arterial blood with oxygen was calculated by dividing oxygen content by oxygen capacity. The blood samples were transferred to oxalated tubes beneath oil and kept in the ice box until analyzed. Analyses were done in duplicate and results which did not agree within five-tenths of 1 per cent were discarded.

The animals were killed while still under the influence of the anesthetic by injecting 10 cc. of a saturated solution of magnesium sulphate into the femoral artery and an autopsy was performed immediately. The position of the rectal catheter was noted and sections of the colon were taken for microscopic study.

Per cent
oxygen saturation
of the arterial blood

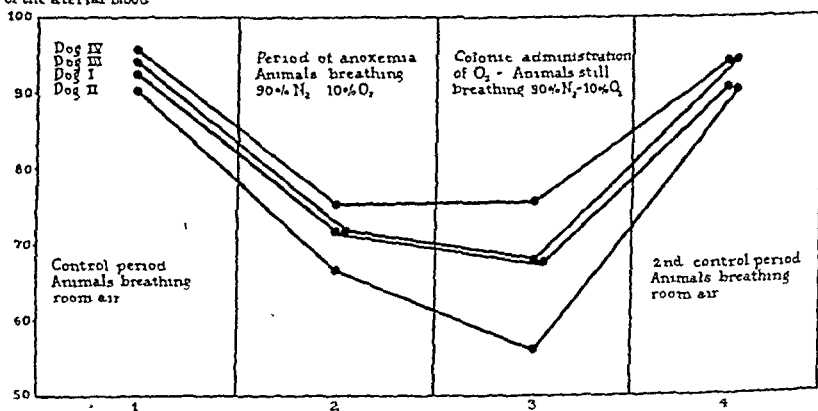


FIG. 2.—Showing that the per cent oxygen saturation of the arterial blood in experimental anoxemia was not increased by the colonic administration of oxygen. The duration of each period in minutes is included in Table 1.

Results. The inhalation of a gas mixture containing 90 per cent nitrogen and 10 per cent oxygen was followed in all of the experiments by a pronounced decrease in the oxygen saturation of the arterial blood. During the control period with the animals breathing room air the oxygen saturation of the arterial blood varied between 90.3 and 95.9 per cent and averaged 93.9 per cent. During the inhalation of the oxygen-poor mixture the per cent oxygen saturation of the arterial blood varied between 66.9 and 75.3 and averaged 71.7. The administration of oxygen, either by rectal tube

TABLE 1.—SUMMARY OF EXPERIMENTAL DATA.

Experiment No. and sex.	Date.	Weight, kg.	Time, minutes.	Conditions.	Arterial blood.			Respira- tory rate per minute.	Pulse rate per minute.
					Oxygen content per cent by volume.	Oxygen capacity per cent by volume.	Oxygen satura- tion, per cent.		
1. Female	January 14, 1931	12.7	1:40	Breathing room air	12.7	13.7	92.7	60	190
			1:50	Breathing 90% N ₂ , 10% O ₂	10.2	14.1	72.3	43	245
			2:01	Administration of oxygen through rectum begun	9.6	14.1	68.1	64	244
			2:19	Breathing room air	12.5	13.8	90.6	54	246
			2:27	Breathing room air	15.8	17.5	90.3	14	134
2. Male	January 21, 1931	23.0	1:37	Breathing room air	11.9	17.8	66.9	19	131
			1:50	Breathing 90% N ₂ , 10% O ₂	10.5	18.7	56.1	18	112
			2:03	Administration of oxygen through rectum begun	15.7	17.4	90.2	10	105
			2:05	Breathing room air	15.2	16.1	94.4	16	102
			3:10	Breathing room air	12.3	17.0	72.3	18	104
3. Male	January 28, 1931	7.6	3:11	Breathing room air	12.2	17.9	68.2	5	102
			3:20	Breathing room air	17.1	18.1	94.5	40	140
			3:50	Breathing 90% N ₂ , 10% O ₂	18.6	19.4	95.9	30	150
			4:04	Administration of oxygen through cecum begun	15.6	20.7	75.3	52	150
			4:21	Breathing room air	15.9	21.0	75.7	46	148
4. Male	February 4, 1931	10.4	4:22	Breathing room air	20.1	21.3	94.4		
			4:45	Breathing room air					
			4:47	Breathing room air					
			5:00	Breathing room air					
			2:40	Breathing 90% N ₂ , 10% O ₂					

or through a cecal catheter, was not accompanied by any significant change in 3 experiments (Nos. 1, 3 and 4). In experiment 2, after prolonged inhalation of the 10 per cent oxygen mixture, the oxygen saturation of the arterial blood fell from 66.9 per cent to 56.1 per cent while oxygen was being given by rectum. It is possible that this was due to the damaging effect of long continued oxygen want on the circulatory system. During the colonic administration of oxygen the saturation of the arterial blood varied between 56.1 and 75.7 per cent, averaging 67 per cent. When the animals were allowed to respire room air again, the oxygen saturation of the arterial blood quickly returned to the control levels. The experimental data are summarized in Table 1 and shown graphically in Fig. 2.

At autopsy it was noted in all of the experiments that the end of the rectal catheter lay in the upper part of the descending colon. There was no gross evidence of trauma. Microscopic examination of the excised sections of the colon did not reveal any significant variations from the normal. Distention of the small intestine was not found in any instance and we were never able to force oxygen through the ileocecal valve after death by using a degree of pressure comparable to that which was employed in the experiments.

Discussion. In accordance with the physical laws of gaseous diffusion, if a gas is to be absorbed from the intestinal tract, it is necessary that the tension of the gas within the lumen of the gut always exceed the tension of the gas in the blood circulating in its wall. If this condition is satisfied the rate of absorption will depend largely on the magnitude of the difference between the two tensions, the diffusibility of the gas in question and the relative permeability of the interposed tissue. The amount of gas which will be absorbed in a given time will be determined by the rate of diffusion and the total area of the exposed surface. In our experiments these conditions have to be considered only in relation to the colon, because the oxygen which we introduced never went past the ileocecal valve to enter the small intestine.

In view of the degree of anoxemia which was produced and the rate at which pure oxygen was administered it is reasonable to assume that a wide difference between the oxygen tension within and without the gut was continuously maintained in our experiments. Therefore, we must look to the other conditions stated above for an explanation of the failure of the animal to absorb oxygen in sufficient amounts and at a sufficient rate to increase the per cent oxygen saturation of the arterial blood. All of these conditions were unfavorable. The diffusion rate of oxygen is low; the permeability of the colonic mucous membrane in all probability is small as compared to that of the thin epithelial lining of the alveolar spaces; the total surface area for absorption is markedly less than that in the lungs and, finally, and perhaps most important of all,

the amount of blood circulating through the colon is a relatively small fraction of the total bloodflow. Doubtless all of these factors, in varying degrees of importance, were responsible for the negative results which were obtained.

Summary. 1. A pronounced drop in the per cent oxygen saturation of the arterial blood of anesthetized dogs was regularly produced by causing the animals to breathe a gas mixture containing 90 per cent nitrogen and 10 per cent oxygen.

2. The colonic administration of oxygen (either by rectum or through a cecostomy tube) did not raise the arterial saturation.

3. Gross and histologic examinations of the colon showed no evidence of injury.

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STUDIES IN REVIVIFICATION.

I. ORGANIZATION OF RESUSCITATION MEASURES.

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THE purpose of the experiments reported in this paper was the establishment of an orderly routine for the resuscitation of animals in which sudden death had been brought about by volatile anesthetics, asphyxia, hemorrhage or electrocution. Since clinical application was the goal of the research, a definite, rigid procedure was developed; a procedure which in our hands resuscitated 82 per cent of our 52 cats, and 52 per cent of our 29 dogs. Early experience demonstrated the necessity of adhering closely to a definite method.

Any variation in the sequence of our procedures made resuscitation more difficult.

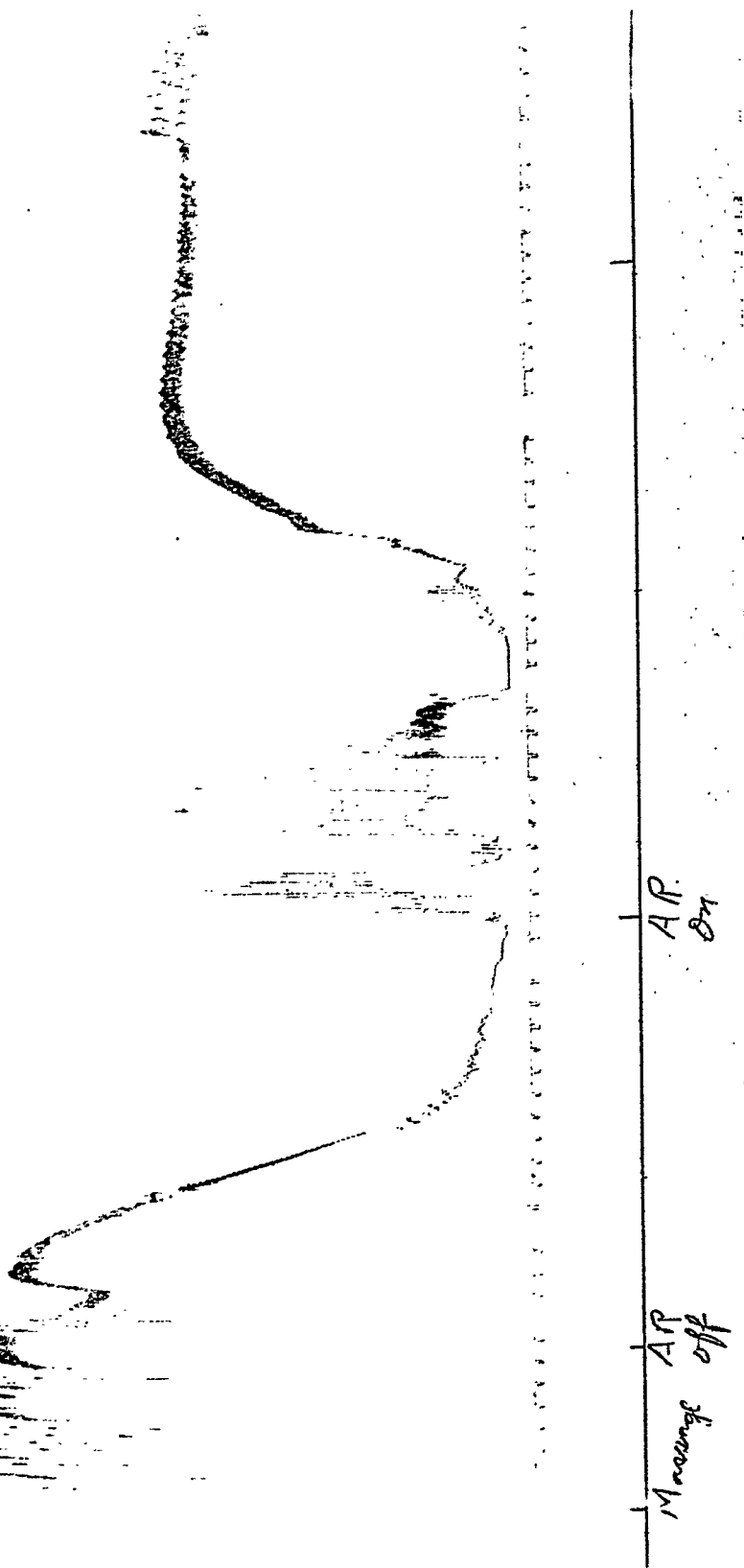
Regardless of the cause of death, the 2 principal conditions to be overcome in resuscitation are respiratory failure and circulatory collapse. Primary circulatory collapse may be due either to cardiac arrest or to central vasomotor paralysis. Respiratory depression may be due to the direct action of a toxic substance on the center, or may be secondary to circulatory collapse. In primary respiratory failure, the heart continues to function for a variable length of time, but eventually dies of asphyxia. Respiratory depression leads to accumulation of carbon dioxid and exhaustion of oxygen. The primary effect of the excess of carbon dioxid in the blood stream is a stimulation of the respiratory center, with a deepening and acceleration of breathing. Excessive stimulation in the presence of oxygen-lack soon leads to paralysis of the respiratory center. The vasomotor center is also very susceptible to asphyxia, but of all the vital centers, it seems to be the most resistant to permanent injury.

In 73 experiments in which an overdose of ether was administered, the respiratory center failed before the heart in 70 (96 per cent), while in 3 (4 per cent) circulatory collapse and respiratory failure occurred simultaneously. When concentrated doses of chloroform were employed, cardiac arrest preceded the respiratory paralysis in every instance. A minimum lethal electric shock invariably produced ventricular fibrillation, in cats, dogs and guinea pigs; respiratory movements continued for varying periods after the blood pressure had fallen to zero.

Despite the fact that the circulatory system may be depressed by one agent and the respiratory mechanism by an entirely different cause, the two systems are normally absolutely dependent one on the other; depression of one invariably affects the other; paralysis of one always results in the ultimate paralysis of the other. It is evident, therefore, that simultaneous treatment for both respiratory and circulatory failure becomes imperative in every instance; the essential problem is to supply oxygen to, and remove carbon dioxid from the tissues.

Experimental Results. Our findings are best described under three headings. In these experiments dogs and cats were given lethal doses of chloroform, ether or electric shock. In some cases, the same animal was killed and resuscitated repeatedly; 1 cat was resuscitated 9 and another 12 times.

SERIES 1. Fifty-three experiments were performed in which resuscitative measures consisted of artificial respiration alone. This measure succeeded in reëstablishing an efficient circulation and respiration in some animals, but failed in others. An analysis of our data showed that artificial respiration was successful in those animals which (because of the absence of pulse, cardiac sounds and



X (see legend)

FIG. 1.—Blood pressure tracing (Hg. manometer) cat. Asphyxial death. Blood pressure falling from 130 mm. to zero; animal pulseless; no cardiac sounds or respiratory movements. Electrocardiogram showed weak auricular and ventricular contractions. Circulation and respiration restored by artificial respiration and manual compression of chest. Time, five seconds. A. R. off and A. R. on = artificial respiration stopped and begun. X = spontaneous respiratory gasp.

respiration) we considered dead (Fig. 1); the electrocardiogram indicated, however, that the heart was beating. Artificial respiration alone always failed to resuscitate the animal, when the respiration was at a proven standstill. Since oxygen is a primary necessity of life, our first consideration was the means of supplying oxygen to the organism; so some form of artificial respiration must be instituted as soon after cardiorespiratory failure as possible. Three different methods of artificial respiration were successively tried. A metal cannula was tied into the trachea, and the depth and rate of respiration were regulated by a Becker interrupter. To obviate tracheotomy, a method of manual compression of the thorax was developed and was found effective. Finally, in order to prevent exhaustion of the operators, insufflation through a rubber catheter introduced into the trachea was adopted. The air blown into the animal was warmed and moistened.

Since at the time of a serious clinical accident, apparatus for carrying out artificial respiration is not always available, the efficacy of various types of manual compression of the thorax was tested. The best results were obtained by using the Schaffer method, modified by placing the animal on its back. Compression of the thorax must be effective in maintaining pulmonary ventilation without, at the same time, doing harm to vital organs. With this type of artificial respiration, too violent manipulation may cause severe injury to the lungs and liver.

The following protocol illustrates the typical results obtained by various measures after complete failure of respiration and circulation.

Experiment 1.—(Fig. 2.) May 26, 1930. Cat, female, 2.3 kg. Carotid artery, femoral vein and trachea cannulized. Blood pressure, 115. mm. Hg.

0:07. Inhalation of excessive concentration of warmed ether.

0:08. Respiration shallow and slow. Blood pressure temporarily fell, then rose above normal. (Asphyxial.)

0:09. Breathing failed; blood pressure dropped to zero; heart feebly beating.

0:10. Heart stopped.

0:11. Mechanical artificial respiration instituted; tight binder applied to abdomen and lower chest; animal placed in extreme shock position.

0:12. Extrathoracic manual compression begun and continued for 1 minute without reinstating natural breathing or arousing the heart.

0:13. Epinephrin (1 to 1000, 0.1 cc. per kg.) injected into femoral vein; no cardiac response.

0:13. Epinephrin driven toward the heart by intravenous injection of saline solution (3 cc.) and by extrathoracic and abdominal massage. The heart immediately began to beat. Blood pressure rose gradually.

0:14. Artificial respiration interrupted at intervals to observe the recurrence of spontaneous breathing. Blood pressure continued to rise.

0:16. First spontaneous respiratory gasp.

0:17. Artificial respiration stopped.

0:18. Regular spontaneous breathing. Blood pressure remained at 150 mm. This was followed by the reappearance of the knee-jerk, voluntary movements and consciousness.

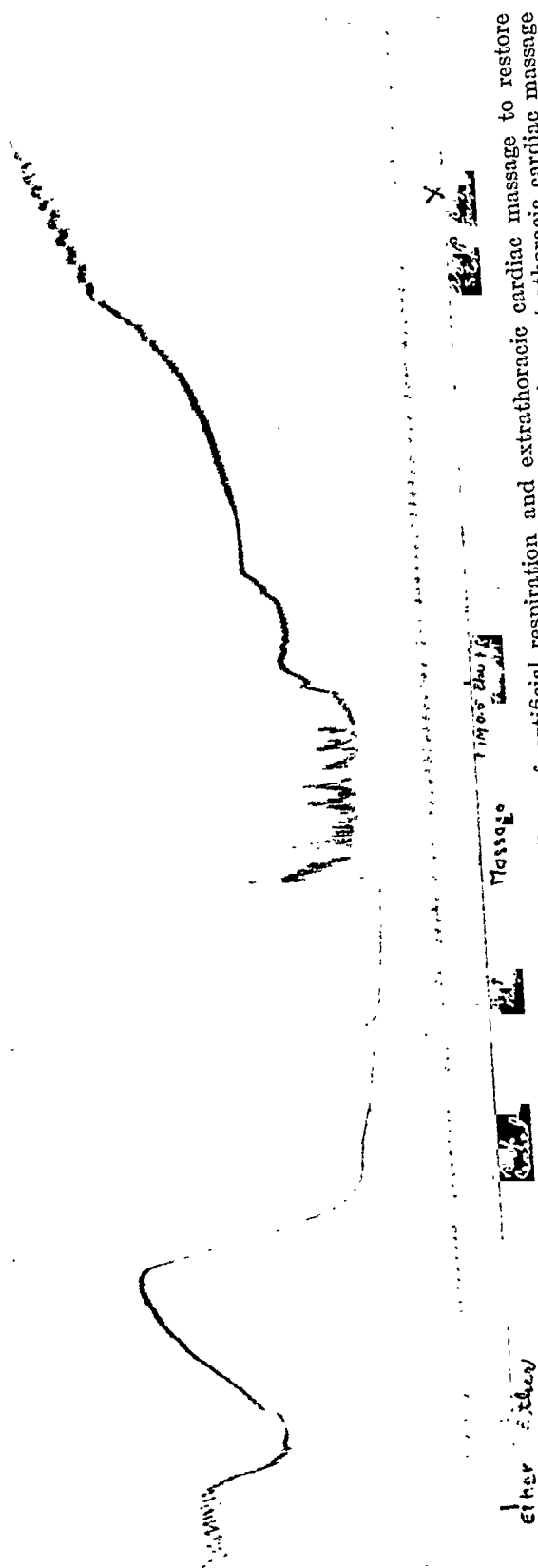


FIG. 2.—Blood pressure tracing of a cat. Ether death. Failure of artificial respiration and extrathoracic cardiac massage to restore the circulation. Successful restoration of circulation and respiration by combination of artificial respiration, extrathoracic cardiac massage and intravenous administration of epinephrin. Blood pressure zero 14 mm. above time marker. Time, five seconds.

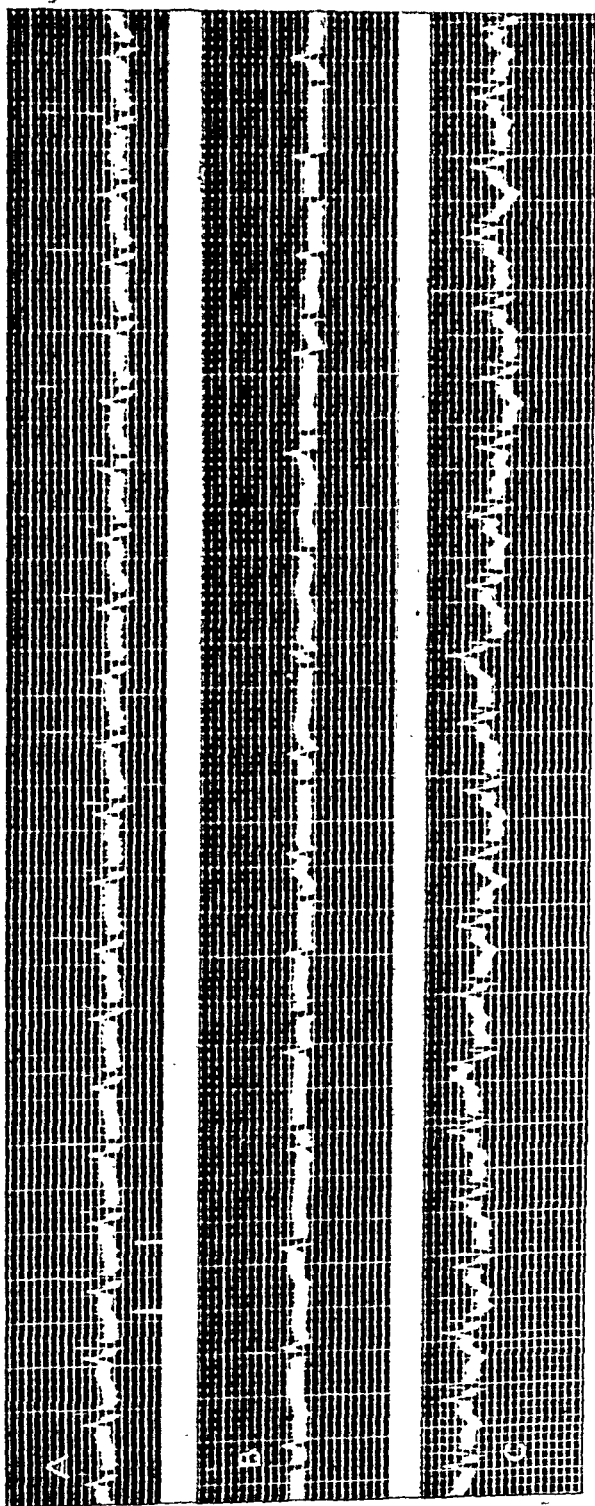


FIG. 3.—Electrocardiograms of cat. *A*, Light ether anesthesia—normal rhythm; *B*, "death" period, when blood pressure was 0 mm. and respiration ceased—complete auriculoventricular dissociation; *C*, recovery, with return of normal blood pressure and reinstatement of spontaneous respiration. N. B.—The R deflections, though faint, are definitely visible in the originals.

In this experiment, in which both respiration and circulation were at a standstill, artificial respiration alone was unsuccessful in reinstating the circulation. However, when the artificial respiration was combined with the administration of epinephrin and an orderly sequence of supportive measures, a complete revivification followed.

Since a feeble cardiac contraction is not generally perceptible by ordinary clinical methods of palpation and auscultation, the heart's action must be observed by direct inspection of the exposed organ or electrocardiographically. Inspection and the electrocardiogram show that the heart may continue to beat coördinately for several minutes after respiration ceases, blood pressure has dropped to zero, and the animal is pulseless. (Fig. 3.) The next phase of the heart's action may be a ventricular standstill, the auricle continuing to beat in orderly fashion until eventually the atrium stops in diastole. Utilizing the electrocardiographic means of determining the condition of the heart, we are able to show that artificial respiration alone is not sufficient to restore to activity a heart all of whose chambers are completely stopped. However, in the presence of any detectable cardiac activity, artificial respiration alone usually restores a useful circulation. Many of the reported successful resuscitations may very well have been of this type.

SERIES II consisted of 44 experiments (25 cats, 19 dogs) in which an attempt was made to standardize a method of inaugurating an artificial circulation which would delay the onset of asphyxia of the central nervous system. A total anemia of the central nervous system rapidly produces irreparable pathologic changes.¹ In resuscitation, therefore, the maintenance of the vitality of the central nervous system through the immediate reinstatement of a circulation becomes of primary importance. Often the heart continues to beat after respiration has stopped and blood pressure has fallen to zero. These slow, weak beats maintain a feeble circulation which postpones asphyxia, and prevents the threatened anemia of the central nervous system.²

Wolff and Lennox² have shown experimentally that cerebral anemia and asphyxia cause vasodilatation of the pial vessels. The first step for increasing the blood supply to the central nervous system is placing the animal in extreme shock position. This change of position favors drainage of the splanchnic area, and immediately encourages a maximal passive blood supply to the cerebral vessels. As an adjuvant to the shock position, tight binding of the abdomen and lower chest decreases the splanchnic blood bed, and assists further in driving blood to the anemic brain. There is a definite technique in applying the binder; pressure is made on the lower abdomen, forcing the viscera against the diaphragm; the binder is then pulled taut across the abdomen and lower chest, and secured with artery clamps from below upward. Artificial respiration in the

presence of the increased intraabdominal and intrathoracic pressure causes effective massage of the heart by the lungs, thus forcing the blood out of the ventricles into the great vessels.

Direct cardiac massage maintains a fairly satisfactory circulation, and helps to delay asphyxia. Since this treatment is impractical clinically, another method of promoting circulation was employed, viz., manual compression of the thorax. With each compression, the heart is emptied, and with each release of pressure the heart refills. Thus the artificial circulation already established by artificial respiration is enormously augmented. Our tracings show that this indirect massage of the heart is as effective in raising blood

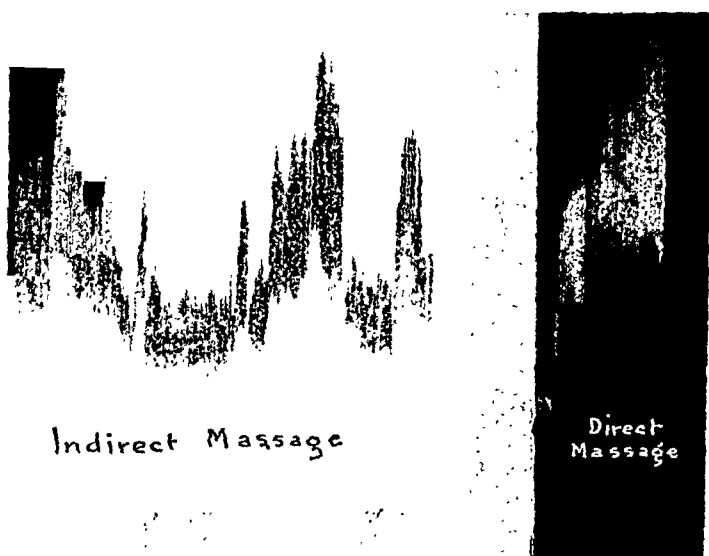


FIG. 4.—A comparison of the effectiveness of maintaining a circulation by indirect cardiac massage (compression of the thorax), and direct massage of the heart.

pressure as is direct massage. (Fig. 4.) This propulsion of blood has been observed in the arteries, veins, and capillaries of the mesentery and the cerebrum of our experimental animals. The circulation thus artificially produced by shock position, abdominal binder, artificial respiration and indirect cardiac massage was sufficient to keep alive the respiratory and vasomotor centers, in several cases, for almost an hour, even though the heart remained absolutely quiescent.

Experiment 2. Cat, male, 3.3 kg. Ether anesthesia. June 18, 1930. Carotid artery, femoral vein and trachea cannulized. Blood pressure, 115 to 125 mm. Hg.

0:03. Electrocardiogram 1. (Normal.)

0:05. Electric shock; blood pressure drops to zero; no pulse nor heart sounds detectable; respiratory gasps.

- 0:06. Electrocardiogram 2. (Ventricular fibrillation.)
 0:07. Respiration stopped.
 0:08. Artificial respiration instituted; animal placed in shock position and abdominal binder applied.
 0:10. Ventricular fibrillation continues.
 0:20. Blood pressure, zero; no spontaneous respiration.
 0:30. Blood pressure, zero; no spontaneous respiration.
 0:50. Blood pressure, zero; no spontaneous respiration.
 0:51. Blood pressure, zero; no spontaneous respiration. Ventricular fibrillation ceases.
 0:51. 0.5 cc. of 1 to 1000 epinephrin injected into femoral vein; 2 cc. 6 per cent glucose wash.
 0:52. Extrathoracic manual massage. No cardiac response.
 0:56. 1 cc. of 1 to 1000 epinephrin injected into femoral vein.
 0:58. Slight cardiac response.
 1:00. Regular coördinate heart beat. Blood pressure rapidly elevated to 90 mm. Hg.
 1:02. Blood pressure falling.
 1:03. Infusion of 1 to 50,000 epinephrin in 6 per cent glucose solution into femoral vein.
 1:03. E. K. G. (Rapid coördinate beat.) Spontaneous respiratory gasps.
 1:08. E. K. G. (Normal rate and rhythm.) This was followed by normal, spontaneous breathing, and a return of the reflexes, consciousness and voluntary movements.

SERIES III. Eighty-two animals (53 cats, 29 dogs) were used to develop the best plan of reëstablishing and maintaining an effective circulation and respiration. The measures already described are incapable of inaugurating or maintaining an efficient circulation; they do, however, retard the dissolution of the vital centers. A cardiac excitant is called for. The extremely consistent stimulatory effect of epinephrin on the accelerator-augmentor mechanism of the heart, and its beneficial pressor effect on the circulation strongly favor its use in resuscitation. The entirely satisfactory results we obtained with this sympathomimetic amin made it unnecessary for us to experiment with any substitute. The dose and the site of injection most likely to restore the circulation had to be determined. Concentrated solutions of epinephrin injected directly into the heart or into a vessel close to the heart often produce untoward phenomena, such as acute cardiac dilation, pulmonary edema, and ventricular fibrillation. Both for effectiveness and convenience, the most satisfactory site for injection was found to be a peripheral vein. Either the saphenous or femoral vein was used in the majority of our experiments. The intensity of the action of epinephrin varies with the state of the vascular system; when the latter is depressed, larger doses are required to elicit a given effect. Volatile anesthetics depress the circulation and diminish its response to epinephrin. In many of our experiments, as much as 0.1 cc. of 1 to 1000 epinephrin per kilo was required to arouse the heart and restore the circulation of animals overdosed with ether, chloroform or electric shock. In many cases, such an amount may prove

excessive; therefore, half this dose is advisable as the initial injection. If there is no response in three minutes, double this amount is introduced into the vein. Exceptions to the use of relatively large doses of epinephrin are a myocardium damaged by chloroform. The rise of blood pressure produced by excessive doses of epinephrin may be great enough to overburden the damaged cardiac muscle, and cause acute fatal dilatation of the heart.

During cardiac arrest the circulation is at a standstill; a minute quantity of epinephrin injected into a peripheral vein is not carried to the heart by the natural circulation; it must be forced into the heart by the rapid injection of a small quantity of fluid. A wash of 3 cc. of fluid in the cat, and of 10 cc. in the dog was found adequate to drive the epinephrin to the heart. Emptying of the veins by their massage toward the heart assisted the movement of the epinephrin. Rhythmic manual compression of the chest wall causes indirect massage of the heart, and forces the blood with its epinephrin through the coronary bloodvessels. In the "dead" animal, compression of the chest wall causes a rise of blood pressure demonstrable on a mercury manometer; the release of this pressure is followed by the return of the mercury to the zero level. This reaction is markedly modified after an effective dose of epinephrin has been administered. Compression of the chest wall then results in a considerably increased excursion of the manometer, and, on the release of the compression, the mercury in the manometer no longer falls to the zero line. When this phenomenon has been achieved, the return of cardiac pulsation is imminent. The initial response of the circulation to the minimal effective dose of epinephrin is a rise of blood pressure to slightly above the normal. When necessary, an efficient circulation is maintained by means of an intravenous infusion of 6 per cent glucose solution, with or without the addition of very minute doses of epinephrin. The rate of the infusion is governed by the fluctuations of the blood pressure. A decided fall of the blood pressure demands an acceleration of the rate of infusion (which, however, should never exceed 3 cc. per minute), and the cautious administration of epinephrin.

If a satisfactory blood pressure is maintained, no further treatment is required except the continuance of the artificial respiration. However, if the blood pressure tends to fall below the normal level, means must be taken to prevent a serious decline. Physiologic saline and Ringer's solutions were tried, but we found neither as satisfactory as 6 per cent glucose. Our routine was to start a slow intravenous infusion of glucose, as soon as the blood pressure fell below the normal level. If glucose failed to maintain the blood pressure at a satisfactory height, small doses of epinephrin were administered repeatedly, or small amounts were added directly to the glucose solution and run into the vein. We consider it important to maintain the blood pressure at an approximately normal level,

avoiding excessive doses of epinephrin. Not only does epinephrin stimulate the heart, and raise blood pressure, but Schmidt and others have demonstrated the advantages of epinephrin as a respiratory stimulant.^{3,4} Our experimental findings tend to corroborate their views. After the reinstatement of an effective circulation an additional injection of epinephrin would often produce a marked rise of blood pressure which was immediately followed by spontaneous breathing.

Depending on the condition of the animal, a variable length of time elapsed between the restoration of the circulation and the appearance of spontaneous respiration. Artificial respiration is interrupted at intervals to ascertain when voluntary inspiratory gasps occur; it is then cautiously discontinued until normal respiratory movements take place, when it is permanently stopped. Natural breathing is followed by a rapid return of the reflexes, and subsequently of voluntary movements and of consciousness. Sometimes it is impossible, with the known means, to reinstate the respiration, even after a normal circulation is established. We are therefore making a comparative study of respiratory stimulants.

Summary. The order of treatment that proved most reliable in resuscitating animals killed by ether, chloroform or electric shock may be summarized as follows:

Place the animal immediately in shock position. Begin artificial respiration by manual compression of thorax until the trachea is catheterized or cannulized. Mechanical artificial respiration is then instituted. Apply the abdominal binder. These procedures require not more than 2 or 3 minutes. Expose and cannulize the femoral vein, and connect it with the glucose reservoir. Inject epinephrin into femoral vein, and wash it to the heart by a small amount of glucose. Reinforce artificial respiration and massage heart indirectly by manual compression of the thorax. If the heart does not recover within 3 minutes, the epinephrin and glucose are repeated. After the heart has begun to beat, blood pressure is maintained at a proper level by the slow intravenous drip of glucose, with or without epinephrin. Artificial respiration is reduced to a suboptimal level; when the animal gasps, artificial respiration is stopped and circulation is supported, if necessary, until consciousness is regained.

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THE SIGNIFICANCE OF THE BARGEN ORGANISM AS AN ETIOLOGIC FACTOR IN ULCERATIVE COLITIS.*

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IN spite of the fact that Bargaen¹ states that the probable etiologic factor in ulcerative colitis is a Gram-positive, lancet-shaped diplococcus which he has recovered after direct proctoscopic examination in 80 per cent of 68 cases, the bacterial etiology of this condition is still a matter of dispute. He also says that the organism can only be obtained by direct proctoscopic culture taken from the depths of an ulcer of the colon after the latter has been thoroughly cleansed by repeated washings and the top of the ulcer has been carefully wiped. Furthermore, cultures of stools failed to yield the organism, though it predominated in cultures of the rectal discharge of mucus, pus and blood. The Bargaen organism has certain distinct cultural and fermentative characteristics. The material obtained during proctoscopic examination is immediately cultured in warm dextrose brain broth,² blood agar and lactose agar and incubated for 24 hours. The organism thus isolated is a Gram-positive lancet-shaped diplococcus growing in twos and fours. A capsule has been observed, thus morphologically the organism resembles a pneumococcus. It is not bile soluble.

In view of the conflicting opinions that have been expressed regarding the significance of the Bargaen organism in ulcerative colitis, it was thought of interest to study the stools and proctoscopic scrapings in a group of 314 patients suffering from a variety of conditions. Approximately 20 per cent of the cultures were from material obtained during proctoscopic examination while in the remaining 80 per cent, cultures were made directly from the feces. Cultures of 4 stomach and 1 duodenal contents were also made. Bargaen's technique was followed, and in addition we streaked progressive dilutions on agar plates. The best results were obtained by following the Bargaen technique.

Statistically considered, the Bargaen organism was encountered twice in 30 proctoscoped cases of ulcerative colitis. In this group, though definite evidence of ulceration was found and cultures were taken from ulcerated areas, no deep extensive lesions were seen. In

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111 cases of spastic colitis of which 22 were proctoscoped and cultures made, and in 89 had stool cultures made, the Bargaen diplococcus was found twice. In these cases no ulcers were revealed by proctoscopy. The Bargaen organism was recovered from 2 of the 22 proctoscoped culture cases. In the group of 173 miscellaneous cases of which 25 were healthy individuals and the remaining 148 suffered from a variety of diseases, 20 per cent of the cultures were taken from material obtained during proctoscopy. These cultures were entirely negative for the Bargaen organism which was only recovered once in the miscellaneous group, and then from the stool of a patient with chronic arthritis having no history or clinical evidence of ulcerative colitis. The typical heat-resistant enterococcus was isolated from 306 cases in the entire series of 314 cases. (See Tables 1 and 2.)

This table shows the varying fermentation reactions of different strains of the enterococcus and the Bargaen diplococcus, without any essential differences between the two types.

TABLE 1.—FERMENTATION REACTIONS.

200 STRAINS OF THE ENTEROCOCCUS.						
	Lactose.	Saccha- rose.	Dex- trose.	Mannite.	Maltose.	Inulin.
90 strains	+	+	+	—	+	—
63 strains	+	+	+	—	—	—
19 strains	+	+	+	+	+	—
28 strains	+	+	+	+	—	—

6 STRAINS OF THE BARGEN DIPLOCOCCUS.						
	Lactose.	Saccha- rose.	Dex- trose.	Mannite.	Maltose.	Inulin.
4 strains	+	+	+	—	—	—
2 strains	+	+	+	+	—	—

+ = Acid
 — = No reaction.

TABLE 2.—DISTRIBUTION OF ENTEROCOCCUS AND BARGEN DIPLOCOCCUS.

30 ULCERATIVE COLITIS CASES.	
<i>Feces Cultures</i>	<i>Proctoscoped Cultures, 30</i>
None made	Enterococcus, 28
	Bargaen diplococcus, 2
111 SPASTIC COLITIS CASES.	
<i>Feces Cultures, 89</i>	<i>Proctoscoped Cultures, 22</i>
Enterococcus, 89	Enterococcus, 20
Bargaen diplococcus, 0	Bargaen diplococcus, 2
173 MISCELLANEOUS CASES.	
<i>Feces Cultures, 132</i>	<i>Proctoscoped Cultures, 36</i>
Enterococcus, 123	Enterococcus, 36
Bargaen diplococcus, 1	Bargaen diplococcus, 0
No enterococcus or Bargaen, 8	
<i>Stomach Cultures, 4</i>	<i>Duodenal Contents Cultures, 1</i>
Enterococcus, 0	Enterococcus, 0
Bargaen diplococcus, 1	Bargaen diplococcus, 0

In 1 specimen of stomach contents cultured, from a case of carcinoma of the cardiac end of the stomach, an organism corresponding in

all respects to the Bargaen diplococcus, was recovered. Stool cultures of the same case did not reveal this organism.

The results which have been presented in the previous paragraphs are at considerable variance with those recorded by Bargaen. Gram-positive lancet-shaped diplococci found in cultures taken as previously described have also been called *Micrococcus ovalis*, *Enterococcus* and *Streptococcus fecalis*³ and must be differentiated from the so-called Bargaen strain by more than microscopic appearance. We experienced no difficulty in isolating the Bargaen organism in the cases in which it was found, either by plating after preliminary culture in dextrose brain broth, or by fishing the small colonies from successive streaked plates. We do not believe, therefore, that in the series of ulcerative colitis cases the Bargaen diplococcus was present and not recovered because of some technical error. We were also able to isolate the Bargaen organism from occasional cases of nonulcerative colitis. No organism was classified a Bargaen diplococcus unless it corresponded to the cultural, fermentative and heat-resistant characteristics described by Bargaen.

In our experience the enterococcus is practically a constant inhabitant of the colon. All of the strains recovered by us fermented lactose, dextrose and saccharose, while there was no constancy as to their reaction on mannite or maltose. The Bargaen diplococci, when isolated, were found to have similar sugar reactions to the enterococci.

The strongest point in differentiation between the enterococcus⁴ and the Bargaen diplococcus is the heat-resistance test. The enterococcus is still viable at the end of one hour of heating to 60° C., while the Bargaen strain is killed at the same temperature. The Bargaen diplococcus seems to be representative of a number of strains of the enterococcus group.

In a series of animal experiments Bargaen⁵ injected 169 rabbits intravenously. Of these animals 56 developed lesions and only 11 of the 56 had received intravenous injections of the Bargaen organism. The other 45 had received mixed cultures of a Gram-negative bacillus ("in all essentials a colon bacillus"—Bargaen does not definitely identify this organism) and the Gram-positive diplococcus. To quote Bargaen, "The lesions in the main were more extensive and the diarrhea more severe in those that had received mixed cultures of the Gram-positive diplococcus and the Gram-negative bacillus."

We have repeated Bargaen's animal work on a much smaller number of animals. Five rabbits which were fed on a normal diet were injected as follows: 2 received intravenous injections of 4 cc. of a 24-hour dextrose brain broth culture of the Bargaen diplococcus, and 2 a 24-hour culture of the enterococcus. The fifth rabbit was kept as a control. The injected rabbits remained healthy, gained weight and at no time showed evidence of diarrhea or other symptoms. At autopsy, 4 weeks after injection, they showed no gross anatomic or microscopic lesions.

In another experiment 10 rabbits were fed for 2 weeks on vitamin-free food (crushed autoclaved oats and water) according to the method of McCarrison.⁶ Four of these rabbits were then injected intravenously with 5 cc. of a 24-hour dextrose brain broth culture of the Bargaen diplococcus and 4 rabbits were similarly injected with 5 cc. of the enterococcus. Two were kept as controls.

None of these injected rabbits exhibited any diarrheal symptoms. Two of the 4 injected with the enterococcus died 10 days after injection, apparently from starvation as did also one of the control animals. The remaining 7 rabbits showing loss of weight and symptoms of malnutrition still being alive at the end of 3 weeks from the time of injection, were then killed and autopsied. In none of these 10 rabbits was there any evidence of intestinal ulceration or gall bladder disease and neither gross anatomic or microscopic sections of the organs showed any significant lesions. Bargaen,¹ injecting 9 rabbits that had been fed on a vitamin-free diet ("crushed oats and water or autoclaved rice, according to the method of McCarrison") with 5 cc. of dextrose brain broth culture of the Bargaen diplococcus, was able to demonstrate lesions in the colon. Of these 9 rabbits all were dead within 5 days. Eight had lesions of the colon ranging from submucous hemorrhages to minute ulcers, and 3 of the 8 had empyema of the gall bladder.

We do not believe that the work reported by Fradkin and Gray⁷ has any clinical significance due to the huge amount of organisms (40 to 50 cc. dextrose brain broth cultures of the Bargaen diplococcus) injected intravenously into their animals over a period of from 5 to 7 days. Furthermore they do not mention using any control animals or control organisms.

Torrey,⁸ in a personal communication to one of us, expresses the same opinion, that the Bargaen diplococcus seems to be an atypical member of the enterococcus group.

Conclusions. The Bargaen diplococcus is a strain of the enterococcus group. It is not regarded as the specific factor in ulcerative colitis since it is not found in every case of this disease and in our experiments not even in a majority of the cases. It can be recovered from cases showing no ulcerative lesions of the colon.

The Bargaen organism was recovered in cases of ulcerative colitis and nonulcerative colitis; from the stomach contents of a patient with gastric carcinoma and from the stool of a patient with chronic arthritis.

The clinician should remember that every Gram-positive, lancet-shaped diplococcus reported found in the stools or from proctoscopic cultures is not necessarily a Bargaen organism. Fermentation reactions, and most important of all, the heat resistance test must be employed before the identification can be made.

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**A CONTRIBUTION TO THE PATHOGENESIS AND HEREDITY OF
THE LAURENCE-BIEDL SYNDROME (DYSTROPHIA
ADIPOSOGENITALIS, RETINITIS PIGMENTOSA,
MENTAL DEFICIENCY AND POLYDACTYLISM).**

REPORT OF THREE CASES IN ONE FAMILY.

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DYSTROPHIA adiposogenitalis, or Froehlich's syndrome of obesity and hypogenitalism, is well recognized. It is usually referred to as a state of hypopituitarism, signifying that the pituitary gland is at fault. In support of this idea are the many instances of pituitary tumors producing this symptom complex. On the other hand, the syndrome occurs in cases where there is no recognizable hypophyseal disorder *per se*. In this category belongs the familial form of Froehlich's dystrophy associated with other hereditary and congenital defects, such as retinitis pigmentosa, mental deficiency and polydactylism. For this clinical picture the name of Laurence-Biedl syndrome was suggested by Solis-Cohen and Weiss.⁵ The constancy of the association of these phenomena is of striking interest because it suggests that obesity and genital atrophy may be inherited genotypic defects, as are the other anomalies found in this condition, namely, supernumerary fingers and toes, retinitis pigmentosa and mental deficiency. Since the latter 3 conditions occur as isolated defects it may be possible that obesity, with or without genital deficiency, may also occur as a single inherited genotypic defect. It is the purport of this communication to add

3 cases of this syndrome to the 42 recorded in the literature and to discuss the pathogenesis and heredity of the disordered mechanisms.

The first paper on the subject appeared in 1866 by Laurence and Moon,¹ in which they describe 4 members of 1 family who showed pigmentary degeneration of the retina, adiposity, genital dystrophy and mental deficiency. Three of the cases showed imperfections of bony and muscular development producing defects in gait. The authors compared the patients to cretins because of their mental deficiency and they recognized the retinal changes as but a part of a general developmental failure.

In 1920 appeared the thesis of Georges Bardet² on a syndrome of congenital obesity associated with polydactylia and pigmented retinitis, in which he describes the case of a girl aged 11 years. He also reviews a case report in 1898 by DeCyon and refers to 2 cases in brothers reported in 1913 by Farnes. Bardet concluded that this syndrome was due to a lesion of both lobes of the pituitary gland during the period of embryonal or fetal development.

Biedl's paper³ in 1922 discusses the syndrome as a distinct one and characterizes it as consisting of obesity, genital hypoplasia, atrophy of the optic nerve with pigmental degeneration of the retina frequently of atypical form, with hemeralopia or night-blindness, polydactylism and inhibition of the mental processes. Two cases in a brother and sister are reported, both having all of the aforementioned symptoms. Four other members of the same family were normal; 2 others died in infancy, both of whom showed polydactylism and who might have shown the complete picture had they lived. A third case in another family is referred to. Biedl states that since the Roentgen films of the sella turcica were normal, the disease is not of hypophyseal origin properly speaking, but of cerebral origin, the lesion being a disturbance of development of the diencephalon in the region of the infundibular area. In 1924 Raab,⁴ from Biedl's Clinic, using the above cases of Biedl in a consideration of hypophyseal and cerebral obesity with genital atrophy, discusses the physiopathology from a mechanical standpoint. He envisages a functional unit in the form of a hypothalamic-infundibular-hypophyseal complex, in which the pars intermedia of the pituitary gland furnishes a secretion. The secretion passes through the posterior lobe and the infundibular stalk to the floor of the third ventricle where certain metabolic and genitotrophic centers are energized. The mechanical factor is in the form of an obstruction to the flow of the secretion through the stalk by an unusually high or massive dorsum sellæ. He states that Biedl has referred to this factor as a strong possibility in the production of cerebral obesity and genital atrophy. He considers the dorsum sellæ defect as a skeletal anomaly similar to that of polydactylism. In addition to this theory Raab considers two others, namely, congenital hypoplasia of the hypophysis and internal hydrocephalus.

From their impressions of the above-mentioned literature and personal contact with Biedl, Cohen and Weiss,⁵ in 1925, proposed the name of the Laurence-Biedl syndrome. They recorded 4 cases in one family of 8, who exhibited marked adiposity with mental deficiency, genital dystrophy and diminution of vision. Two of the affected children showed polydactylism; the eye grounds showed a typical retinitis pigmentosa. In their discussion they state that an hypophyseal lesion cannot be proved; that Roentgen ray examinations of the sella region do not show conclusive changes. No anomaly of osseous development is found (except polydactylism). Sugar tolerance tests do not indicate pituitary disease. Basal metabolic studies were below normal in 3 of the children. Parents and children gave negative Wassermann reactions. Cohen and Weiss refer to Raab's ideas as most attractive, but prefer to keep an open mind on the pathogenesis of the syndrome until more conclusive evidence is presented.

Bernhardt,⁶ in 1928, states that only about 20 positive observations of this syndrome have appeared in the world's literature. He reports 2 new cases in brothers aged 16 and 10 years respectively. Both boys had visual impairment from the age of 18 months and a Froehlich's type of adiposity with hypogenitalism. One had polydactylism and a permanent severe nystagmus; the other a pronounced tower-shaped skull, unilateral cryptorchidism, genu valgum and severe nystagmus. The latter also had positive evidence of a moderate degree of diabetes insipidus. Sellar Roentgen rays were negative; basal metabolic rates were normal. In the summary he states that these cases present a primary disturbance of development, the principal seat of which must be looked for in the hypophysis, midbrain and optic nerve region complex. In accord with Biedl, he considers this syndrome as a special case of the so-called cerebral form of the Froehlich adiposogenital dystrophy. He mentions a case report of von Jaksch in 1912.

In the same year appears Boenheim's⁷ contribution in which he adds to the cardinal characteristics of the syndrome, hardness of hearing, malformations other than polydactylism, and perhaps cutaneous pigmentation. He states that psychical disturbances belong to the classical picture, especially in the form of dementia, and were observed by him in some of the cases, whereas in others it was absent. Boenheim accepts the tenets of Biedl and Raab as probable causative factors. He reports 4 cases, 2 of which were familial. One brother had adiposity, polydactylism, arrest of mental development and acromegalic tendencies of the hands and feet; he was aged 28 years. The other brother, aged 36 years, had hemeralopia with retinitis pigmentosa, genital hypoplasia, mental retardation, but was small and slender. The author remarks that the entire clinical picture in these 2 cases could be elucidated only through connection of each case with the other.

A third paper appeared in 1928, that of Ricaldoni and Isola.⁸ Four more cases are described in one family ranging in age from 12 to 21 years. All of the cardinal manifestations were present in the 4 cases and the impaired vision began in each one at a very early age. In 1 child there was a moderate degree of hemiatrophy of the entire body. All 4 were very timid, very emotional and of poor intelligence. Serologic and urine tests were all negative. Roentgenograms of the skulls in all 4 patients showed a small sella turcica with very long clinoid processes covering the sella like a roof. There was no retardation of ossification or fusion of the epiphysis of the long bones. The family history was very interesting. The parents were first cousins and apparently healthy. Ancestrally, there were several blind individuals in the maternal line and several obese ones in the paternal line. There were 4 unaffected children in the present family, but 1 died seven days after birth and had an imperforate anus; another had a distended abdomen and died 2 days after birth; a third was a stillbirth. The authors, judging from the smallness of the sella turcicas, reason that the lesion is in the hypophysis. But, they say, if the malformation of the sella was the primary cause of the condition, it would have been found in the other reported cases, and this has not always been true. They emphasize the familial character of the disease and say that direct transmission of the syndrome has not been seen because the patients are almost all of necessity infertile. It is their opinion that the adiposogenital dystrophy is the primary and necessary symptom of the syndrome; the retinitis and polydactylia are not necessarily present and that there are formes frustes without one or both of them. The most incomplete form is that with adiposogenital dystrophy alone, which is a dysplastic congenital form of the dystrophy as opposed to the purely accidental type of Froehlich-Babinski. And one of the characteristics of the congenital form is that it is usually associated with retinitis and polydactylism, showing that it is embryonic in origin, while accidental dystrophy is generally accompanied by symptoms showing irritation or compression of the brain or the region adjacent to the hypophysis.

A paper by Rieger and Trauner,⁹ in 1929, is entitled "A Case of Biedl-Bardet Syndrome and the Hereditary Relations of This Condition." Their case presents in brief the following features: A girl, aged 6 years in 1925, showed marked adiposity, retinal degeneration and hyperdactylia, infantile genitalia, normal mentality, hyperextensibility of the wrists; medium-sized normal sella. Consanguinity in the parents is present. An older child developed multiple sclerosis; a younger one died at 6 months, was fat and had a supernumerary toe. A number of fat people exist in both branches of the family. These authors do not accept the theory of hypophyseal secretory disturbance of previous authors, nor that of cerebral

disease with primary changes in the skeleton expounded by Biedl and Raab. They believe the disease is genotypic in nature. This is confirmed by the fact that in each case the three main symptoms of the syndrome are characteristic, each one of them being of an hereditary nature.

deSchweinitz,¹⁰ in his Bowman lecture, speaks briefly of the association of pigmentary degeneration of the retina with pituitary diseases and polydactylism. He mentions 3 cases of this character that he has himself observed. A case of Chaillous¹¹ is interesting because a girl, aged 4 years in 1914, with enormous obesity, polydactylia and defective vision, had normal eye grounds, but in 1919 the evidence of retinitis pigmentosa was found. Roentgen ray of the sella was normal. Chaillous mentions a case reported by Bertolotti in 1914. McAlpine¹² describes a case of a boy aged 16 years, showing all of the characteristic phenomena. A brother and sister affected by this condition are reported by Beck;¹³ and Lisser¹⁴ reports the case of a girl, aged 8 years.

Serejski,¹⁵ contributing to the Biedl Jubilee number dedicated to Dr. A. Biedl on the occasion of his sixtieth birthday, writes of the Laurence-Biedl syndrome and reports a case. He attempts to include this syndrome in the same group of heredodegenerations in which amaurotic family idiocy belongs. Other case reports have been made by Denzler,¹⁶ Deusch,¹⁷ Lange¹⁸ (4 cases), von Ratner¹⁹ and Bauer.²⁰ In the ancestry of Deusch's case, a paternal uncle had polydactylism and several others in the father's family exhibited adiposity.

Report of Cases. CASE 1. There are 6 children in this family, 3 of whom are affected with the condition under consideration: Milford, aged 12 years, the second born; Margaret, 2½ years, the fifth born; Helen, 1½ years, the last born. They are very obese, mentally retarded and hemeralopic, but they do not have polydactylism. The birth was uneventful in each instance and there occurred no infectious illness or convulsions in infancy.

Milford weighed 8 pounds at birth and at 3 months weighed about 10 pounds more than he should. At this age he apparently observed objects as a normal child and did not manifest evidence of impaired vision until about the fifth year. Gain in weight has been constant, at present he weighs 140 pounds. Visual impairment is very marked and he has the symptom of night blindness (hemeralopia). He can read ordinary print, holding the page about 8 inches away, but only in bright daylight. He has no difficulty in finding his way in daylight or in a brightly-lit room, but on entering a dimly-lit corridor he gropes about because he cannot discern objects about him. It goes without saying that he has the greatest difficulty in finding his way at night. He is mild-mannered, quite stable emotionally but is mentally retarded, lacking the spontaneity and ready responsiveness of a boy aged 12; there is no qualitative mental defect, however. Evidence of polyuria, polydipsia or excessive appetite is lacking. (Figs. 1 and 2.)

The obesity is of the Froehlich type. The abdomen is rounded and protuberant with increase of girdle and suprapubic fat. The breasts are very prominent; the proximal portions of the extremities are well-rounded as in the female and there is a marked degree of genu valgum and pes planus.

The genitals are extremely underdeveloped and truly infantile; the scrotum is very small and without the normal contents; testes could not be palpated in the inguinal canals. There is not a trace of axillary or pubic hair. Pupils and extraocular movements are normal but with a fine nystagmus laterally. The optic disks are grayish; the vessels of the fundus are reduced in size.

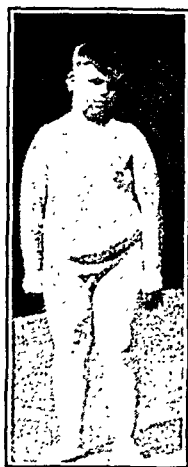


FIG. 1.—Case 1. Showing Froehlich type of adiposity.

The retinae show a pigmentary degeneration of atypical character with uncovering of the choroidal circulation. Vision is O. S. 5/100, O. D. 5/150. The sella turcica is normal in all respects, measuring 10 mm. by 6 mm. The deep and superficial reflexes are normal. The blood and urine studies were entirely negative; sugar tolerance test and basal metabolic rate were normal. Water intake and output were not abnormal and blood Wassermann was negative.

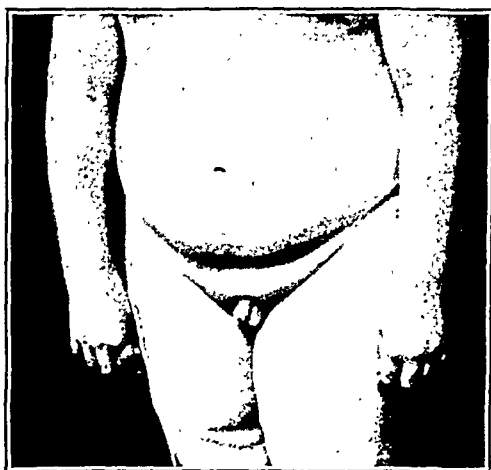


FIG. 2.—Case 1. Showing hypogenitalism.

CASE 2. In Margaret the visual defect was suspected and looked for earlier because of the parents' experience with the first case. It was noted that in the third or fourth week after birth the child's visual attention could not be held and that its eyes flitted about more than in the normal children

and that the pupils were very large. She slept more than did the normal children. She has not learned to walk. The obesity is extreme, the fat hanging in folds around the trunk and limbs. Margaret is so unwieldy-looking that one is not surprised to hear that she prefers to remain in a sitting posture for hours rather than move. There is a definite mental



FIG. 3.—Roentgen ray of sella turcica in Case 1, showing no gross deviation from normal.

defect recognizable even at this early age. She is afraid of strangers and becomes panicky when approached or spoken to. She will not answer except when one refers to food, then she will nod her head. Her appetite is excessive and the intestinal evacuations are almost of adult quantity. Polyuria and polydipsia are not present. The retinal and optic nerve

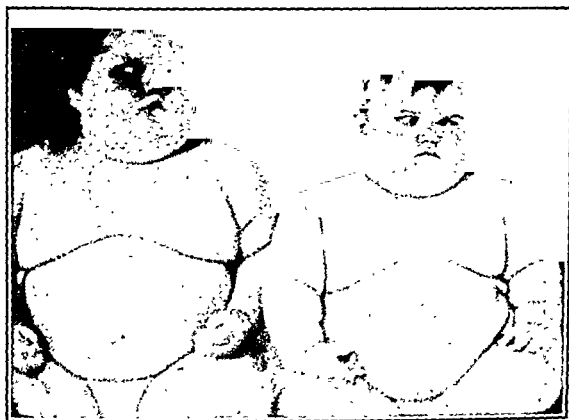


FIG. 4.—Cases 2 and 3.

changes are similar to those present in Milford. A moderate nystagmus is observed; sella turcica is normal and all blood and urine studies are negative.

CASE 3. The visual defect in Helen was observed from birth and it is stated that her eyes were more restless than in the other two. The pupils were dilated from birth. The atypical retinitis pigmentosa is also present.

Her adiposity is even greater than that of Margaret. At 12 months she looked like a 2-year-old because of her size. The fat hangs in folds about her body and limbs. The same mental and emotional defect is observed as in Margaret. The clinical studies were also negative as in the other 2 cases. The question of genital development could not be determined in the younger cases at their present ages. Their vision could not be tested for the same reason. Roentgen examination of all 3 cases showed no change in osseous development. No other congenital anomalies or defects were observed. (Fig. 4.)

The 3 normal siblings are a 15-year-old boy who is small in stature and not fat; a 10-year-old girl, normal in size, vision and intellect; a 5-year-old boy, light in weight. The family history is interesting in that several paternal ascendants have been overweight and tall; a grand uncle weighed 338 pounds and was 6 feet tall; the grandfather weighed 190 pounds and 4 grand aunts and uncles each weighed about 200 pounds. But no one had visual, mental or developmental defects. There is no consanguinity in the parents.

Discussion. From a critical review of the literature one is impressed with the fact that all of the observers are agreed that the syndrome of Laurence-Biedl is an hereditary and familial disorder. That the symptoms of hemeralopia (retinitis pigmentosa), the polydactylism, the feeble-mindedness and the less frequent anomalies reported are unquestionably inherited defects of genotypic character. But unanimity of opinion as to the nature of the adiposogenital dystrophy is lacking. It was natural for the earlier observers to look to the hypophysis for the explanation, namely, Bardet: a lesion of both lobes of the pituitary gland during the period of embryonal or fetal development. Since the roentgenographic sella turcica findings have not been grossly or constantly abnormal except for the occasional finding of a massive and high dorsum sellæ, Biedl and Raab did not feel that the hypophysis was at fault. Instead, they suggested a dysfunction of the hypothalamic region due to the failure of the secretion of the pars intermedia of the hypophysis to reach the floor of the third ventricle to energize certain genitotrophic and metabolic centers because of compression and obstruction of the infundibular stalk by the high and massive dorsum sellæ. Thus Biedl differentiated between a pituitary type and a cerebral (hypothalamic) type of Froehlich's adiposogenital dystrophy. The anomaly of the dorsum sellæ was considered as another expression of defect in the skeleton as the polydactylia. Timme²¹ has expressed a similar thought when he stated that "such an anatomical characteristic, as defective conformation of the base of the skull, can be much better understood as being a unit factor in inheritance than can the complicated biochemical process leading to the superficial picture we see."

This theory is not sufficiently impressive to be accepted without further analysis. If the osseous anomaly be the unit factor conditioning the appearance or nonappearance of the fat and genital dystrophy, then the occurrence of the latter would not be so constant

a feature of the syndrome, because the dorsum sellæ is as often normal in these cases as it is abnormal. Also, sella malformations should in some instances interfere with the function of the entire hypophysis and occasionally produce other types of dyspituitarism such as dwarfism, gigantism or acromegaly which, however, are not parts of the Laurence-Biedl picture. Therefore, one must look to regions which characteristically give rise to disturbances of fat metabolism and hypogenitalism, namely, the hypothalamic region of the diencephalon.

In certain cases following epidemic encephalitis, dyspituitary syndromes—excessive adiposity, increased carbohydrate tolerance, genital dystrophy—are sometimes observed. The pathologic evidence that the pituitary gland is ever involved in epidemic encephalitis is very slender. On the other hand, with the well-known predilection of the virus of epidemic encephalitis to involve the gray matter of the midbrain, the nuclei of the hypothalamus might well be involved. Urechia and Elekes²² examined the brain of a case of adiposogenital dystrophy with polyuria and found a marked internal hydrocephalus and sclerotic foci of an old encephalitis in the hypothalamus. The hypophysis was normal while the tuber cinereum was compressed and thinned by the intraventricular tension, and the nuclei of this region showed marked cellular lesions.

Recent research has indicated that many symptoms formerly ascribed to a lesion of the pituitary body itself may result from lesions involving the closely related hypothalamic region of the brain. Camus and Roussy²³ claim to have produced typical dyspituitary syndromes in dogs by injury to the tuber cinereum above the pituitary glands, the latter being left intact. Similar results were obtained by Aschner²⁴ and Bailey and Bremer²⁵ indicating, as first suggested by Erdheim, that a disturbance of the hypothalamus may be the cause of many of the symptoms attributed to pituitary derangement. Roussy²⁶ states that certain tuber nuclei regulate the fat, others the sugar and water metabolism; their lesion is followed by Froehlich's syndrome, which could not be produced by removing the hypophysis without a lesion of the tuber cinereum. In his experiments on 149 dogs and 46 cats, Roussy has checked up earlier publications and has found new facts which support his conception of the rôle of the vegetative centers of the region of the tuber cinereum.

The occurrence of obesity after experimental lesions confined to the hypothalamus has been observed by many workers. Gournay and LeGrand present evidence that the paraventricular nucleus is the structure damaged in animals developing obesity. Genital atrophy is usually associated with obesity which results from a hypothalamic lesion. Camus and Roussy contend that obesity never results from a lesion confined to the pituitary gland, but is always due to a lesion of the tuber cinereum, but as Cushing points

out, it is difficult to believe that the obesity associated with a pituitary tumor which remains absolutely confined within its dural capsule can possibly be produced in this way. Cushing and Maddock have shown that adiposity can be produced by obstructing the infundibulum.

In this somewhat controversial situation, Collin²⁷ warns that, in his opinion, the overestimation of the vegetative centers in the hypothalamus without taking into consideration their correlation with the hypophysis will prove as one-sided as was the former endocrinologic point of view. This advice is particularly striking when we recall that the posterior lobe of the pituitary is developmentally a protrusion of the tuber cinereum, and that in the fully-developed animal nerve fibers are seen running from one to the other. It becomes, therefore, a justifiable speculation to consider both as parts of the same complex neuroglandular mechanism. If, therefore, the hypothalamus becomes, in certain instances, the seat of an embryonal developmental defect, then it is reasonable to expect a dysfunction of the neuroglandular complex under consideration.

The adiposogenital dystrophy of the Laurence-Biedl syndrome is of this order, the embryonal defect involving the diencephalon. In the development of the nervous system each stage is identified with the activity of certain specific genes. The genes concerned with the evolution of the ventral portion of the ectopic zone of Schulte surrounding the optic vesicles which gives rise to the hypothalamus, are abnormal. They are transmitted through the germ plasma and produce an inherited diencephalic defect as a unit character.

The almost constant association of retinitis pigmentosa and feeble-mindedness with the Froehlich syndrome in the Laurence-Biedl picture is explained on this basis of a genetic defect of the prosencephalon. In the early stages of the neural tube the first segment of the encephalon is the forebrain (prosencephalon). This division of the brain develops two large evaginations, the optic vesicles, from which are derived the retinae of the eyes. A narrow, circumferential area of the forebrain surrounds the optic vesicle on its dorsal, cephalic and ventral aspects and is called the ectopic zone, from the three areas of which the end brain together with the several parts of the interbrain take on form. From the dorsal area develop the epithalamus, thalamus, subthalamus and geniculate bodies of the diencephalon. From its ventral area the hypothalamus takes origin. The cephalic area of the ectopic zone gives rise to the end brain.

The optic vessels gradually become the optic cup and stalk which retains connection with the ventral segment of the ectopic zone. The stalk eventually serves as the framework through which the developing fibers of the ganglion cells of the retina pass to form the optic chiasm. The remainder of the ventral segment of the

ectopic zone gives rise to the other chief constituent of the hypothalamus, namely, the infundibular region from which differentiates the tuber cinereum including the bulbous infundibuli, infundibular process and stalk, the lateral eminences and the postinfundibular eminence (Tilney and Riley²⁸).

It is seen, therefore, that the development of the infundibulum, the optic chiasm and the retinal fibers is an intimate one in that the ventral segment of the ectopic zone gives origin to all of them. Therefore, a defect in the character of the genes responsible for the laying-down of the various steps in the evolution of the ectopic zone in its ventral segment may result in an abiotrophic condition of the infundibulum, optic nerves and retinae. The infundibular defect results in the Froehlich picture, the chiasmatic defect produces the optic atrophy, and the pigmentary degeneration of the retina is explained not by abnormal ganglionic-cell development but through involvement of certain fibers in the optic chiasm. The authority for this statement is the following from Tilney and Riley:²⁹ "Not all of the fibers of the optic chiasm are afferent in their course, some being efferent from the visual cortex as well as from the superior colliculi. To these fibers has been attributed the function of governing chemical changes which occur in the retina and also movements in certain elements of the retina, the retinal pigment cells." Ranson³⁰ states that "the optic nerve also contains some efferent fibers which terminate in the retinae. (Arey, 1916.)"

Since the cephalic segment of the ectopic zone gives origin to the end brain, it may be that the defect in intellectual development is a part of this segmental embryonic deficiency.

The relatively new sciences of genetics and experimental embryology have advanced positive and inescapable experimental evidence proving that the chromosome is a structure composed of many diverse parts, each part or gene having a definite effect on development and therefore, a definite effect on the characteristics of the individual produced. Much of this evidence has come from the investigations on the common fruit fly, *Drosophila melanogaster*, the organism whose heredity is best known. It has been found that at least 50 pairs of genes coöperate to produce the normal red color of the eye; if any one of these 50 genes is altered, or is defective, the eye color will be diverse from the normal. The same situation is found for all characteristics. Another defective gene in *Drosophila* causes the animals to produce reduplicated legs. This is due to a gene in the X-chromosome, so that the abnormality shows sex-linked inheritance. A modified gene in the X-chromosome near its left end, causes the fruit fly to grow to nearly twice the size of ordinary *Drosophilas*; individuals without this gene do not become giants, no matter how well fed. (Jennings.)³¹

In man, differences in body-build (stoutness and slenderness) are often due to gene differences (Davenport).³² Structural abnormal-

ities of certain kinds are usually or always due to gene peculiarities such as polydactylia. Therefore, from the viewpoint of genetics, single unit characters such as polydactylia, mental deficiency, obesity, thinness, color blindness, deafness, retinitis pigmentosa, and others, are readily conceived as inherited traits. But when several occur together often enough to be considered as a distinct clinical entity, one must explain the association either as a chance coupling of unit characters or on the basis of a genetic defect involving a developmental center of wider and more far-reaching influence. This is the case in the Laurence-Biedl syndrome. The adiposogenital dystrophy, retinitis pigmentosa and mental deficiency are related to a genetic defect of the ectopic zone in its cephalic and ventral segments; in other words, a cerebral genotypic unit character. The polydactylia, skull deformities, atresia ani and other occasional anomalies are present only through the accidental coupling of somatic genotypic unit characters.

Summary. 1. Adiposogenital dystrophy, retinitis pigmentosa and mental deficiency are the most constant phenomena of the Laurence-Biedl syndrome in the order given; polydactylism is next and other anomalies of development last.

2. This form of Froehlich's dystrophy is considered herein to be a genotypic inherited unit character defect, because the associated symptoms of the Laurence-Biedl syndrome are found occurring as isolated manifestations of the same order.

3. The frequent association of the first three elements of the syndrome is explained on the basis of a developmental defect of the ectopic zone of the prosencephalon, for the embryological reason that the hypothalamus (infundibulum) and the optic chiasm take origin from the ventral segment and the end brain from the cephalic segment of the ectopic zone of Schulte.

4. The other developmental anomalies, namely, polydactylism, skull deformities, atresia ani, and others, appear because of the coupling of somatic genotypic defect characters with the cerebral units characters mentioned above.

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CEREBRAL ADIPOSITY WITH NERVE DEAFNESS, MENTAL DEFICIENCY AND GENITAL DYSTROPHY: A VARIANT OF THE LAURENCE-BIEDL SYNDROME.

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IN 1925 Solis-Cohen and Weiss¹ reported 4 children of one family who exhibited marked adiposity with mental deficiency, genital dystrophy and diminution of vision due to retinitis pigmentosa. Another anomaly, polydactylism, was present in 2. The fat distribution was of the Fröhlich type. Roentgen ray examinations of the sella region did not show conclusive changes nor in any other way could a pituitary lesion be proved. Four unaffected children in the same family were entirely normal.

Search of the literature revealed a remarkably similar family group reported by Laurence and Moon² in 1866. Many years later (1922) similar cases were recognized as a syndrome by Biedl.³ In this and a subsequent communication* he discussed the condition as a familial form of dystrophia adiposogenitalis of cerebral rather than pituitary origin.

Because of the original description by Laurence and Moon and

* Personal communication, 1924.

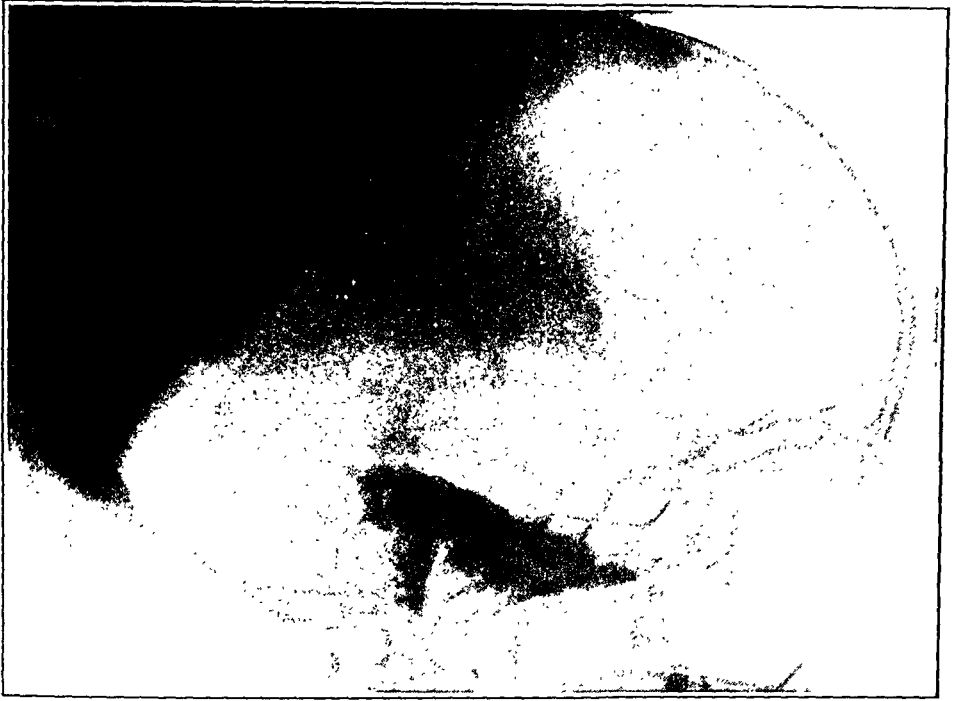


FIG. 1.—Normal, or possibly slightly smaller than normal sella.

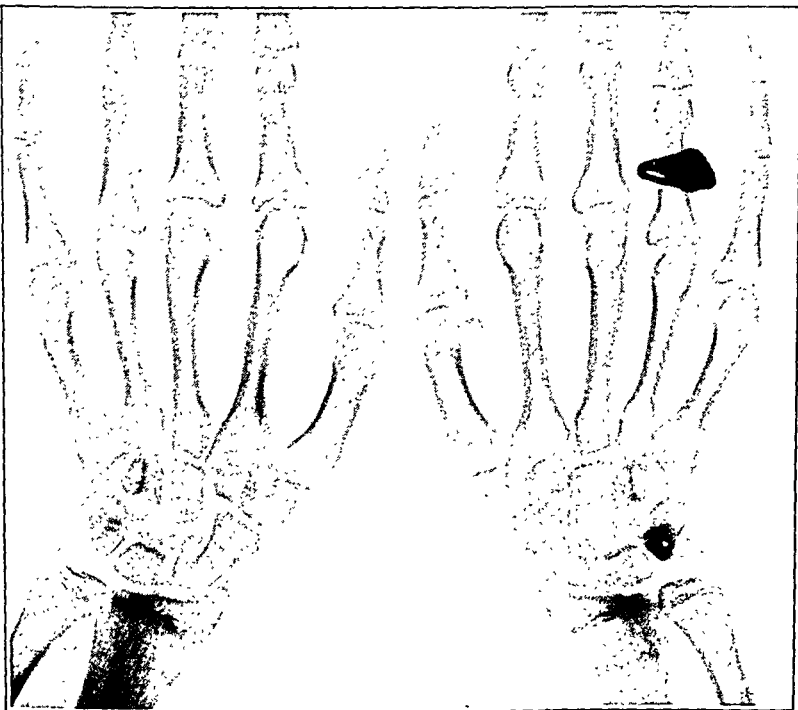
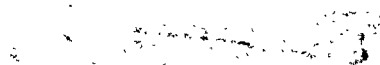
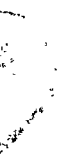


FIG. 2.—Normal osseous development in hands and wrists.



the elaboration as a distinct cerebral obesity syndrome by Biedl the name Laurence-Biedl syndrome was suggested for the condition.

Many cases of the fully developed syndrome have since been reported (the total is now 45), a complete bibliography of which is included in an excellent article by Ornstein,⁴ who adds 3 cases in a contribution to the pathogenesis of the syndrome. Another case recently has been described by McCrae and Weiss⁵ and in a separate article made the basis of a discussion of pathogenesis and treatment by Weiss.⁶

The present report has to do with 2 cases in sisters who present cerebral obesity, mental deficiency, nerve deafness and genital dystrophy, apparently a variant of the Laurence-Biedl syndrome, in which deafness takes the place of retinitis pigmentosa.

Case Reports. CASE 1.—C. C., a white girl, aged 16 years, was first observed in 1924 because of defective hearing and retarded growth. She also was troubled at times by psoriasis.

The family history was unimportant except that someone in the father's family was said to have had 6 fingers.

The patient was the youngest of 4 children, born slightly prematurely, but apparently a normal infant at birth. Teething, walking and talking occurred normally. She had chickenpox, measles and occasionally a head cold, but never suffered from sore throat. When the child was about 6 years of age the mother noted that the hearing was poor and an adenoid operation was done. The hearing did not improve. She had rheumatic fever at 12; was in bed for 1 week and confined at home for 10 days. At the age of 13 she had an attack of paratyphoid fever. She had never gotten along well at school, had always been backward in her studies and at the age of 16 was in the 8th grade. She had never menstruated.

She was 55½ inches tall and weighed 109 pounds. The span was 54 inches. Symphysis to vertex measured 27¾ inches; symphysis to sole 27¾ inches. There was somewhat excessive girdle adiposity and the breasts were very large. There was very little hair on the genitalia and no hair in the axilla. There was psoriasis on the hands and feet. The tonsils were large and the postcervical glands were slightly enlarged; otherwise the general physical examination gave no findings of importance. The eye grounds were normal, showing no evidence of retinal degeneration.

Gynecologic examination showed a small and conical cervix and a retroverted and antiflexed uterus. The diagnosis was genital hypoplasia of moderate degree.

The ear examination showed evidences of bilateral chronic catarrhal otitis media and marked loss of hearing due to nerve deafness.

Roentgen ray studies showed a sella possibly slightly smaller than average (Fig. 1). The bones of the skull otherwise were normal. No changes were observed in the bones of the forearms and wrists (Fig. 2). There was a possibility of slight thymic enlargement. Basal metabolism was +24 per cent. Sugar tolerance figures were 121 mg. before administration of glucose, 192 mg. at 1 hour and 123 mg. at 2 hours afterward. The blood Wassermann was negative. The urine was normal. Blood count was recorded as hemoglobin, 80 per cent; red blood cells, 4,650,000; white blood cells, 14,000; the differential count showed polymorphonuclears, 57 per cent; lymphocytes, 39 per cent, and monocytes, 4 per cent. The blood pressure averaged 110 systolic and 60 diastolic. Temperature, pulse and respirations were normal. The patient remained under observation

for about a year and a half and received thyroid, pituitary and ovarian substance during that period. Beneficial results were questionable. She did not increase in height; for a time the weight was slightly reduced, but later returned to the previous level; scanty menses occurred on three occasions at very irregular intervals; there was a slight growth of hair over the genitals but none in the axilla. Hearing did not improve and there was no improvement in schoolwork. Toward the end of this period of observation tonsillectomy was performed with satisfactory convalescence but apparently without benefit to her hearing.*

CASE 2.—A sister, aged 26 years, likewise presented adiposity, mental deficiency, deafness and insufficient menstruation. Like the other child she was born slightly prematurely. She weighed 6 pounds at birth. She was a delicate infant; teething at the normal age; talked at about 14 or 15 months; and began walking at about 2 years. Deafness was discovered at the age of 10 or 11. Adenoid operations were performed at the age of 13 and again at 17. The mother thinks that the hearing improved slightly after the second operation. During infancy and in childhood the mother states that this child had some sort of spells; her body would "stiffen out," but since menstruation she had had none of these attacks. Menstruation did not begin until about 17. It had been fairly regular but never sufficient in amount. She was operated on for appendicitis at the age of 20. She never got along well at school, was in the 6th grade at the age of 17 and then quit.

She was 5 feet tall and weighed 142 pounds. There was a high-arched palate, girdle adiposity and very large breasts. The mother stated that she had always been stout and also mentioned that the difficulty in hearing was especially with the left ear and that this was true of the first child as well. This patient spoke with difficulty and had a kind of muffled speech. The general physical examination gave no findings of importance other than those mentioned. The patient presented herself only once and would not permit further study.

The 2 middle children of this family were slight. The hearing was good and they seemed perfectly normal.

Discussion. From a study of our cases and a review of the literature it seems clear that the Laurence-Biedl syndrome is a congenital and familial form of cerebral adiposity associated with mental deficiency, genital dystrophy, retinitis pigmentosa and frequently polydactylism. The recorded cases resemble one another very closely, a distinctive feature being the familial occurrence. In fact, Boenheim⁷ states that cases can be placed in the Laurence-Biedl group only if familial. He also calls attention to the fact that one or another of the chief symptoms may be absent and that not all cases show the complete picture of the Laurence-Biedl syndrome as above described. In addition he mentions *hardness of hearing* as a cardinal characteristic of the syndrome.

The early students of the subject considered a lesion of the pituitary gland responsible; Biedl and Raab⁸ discussed the development of the disorder from a mechanical standpoint suggesting that a high and massive dorsum sellæ (a skeletal defect which they consider

* The patient was last heard from July, 1931. The height remained the same; weight, 124 pounds; hearing had not improved, and the menses still were very irregular.

similar to that of polydactylism) interferes with the flow of an energizing secretion from the pars intermedia of the pituitary gland through the stalk of the infundibulum to certain metabolic and genitotropic centers at the floor of the midbrain.

Just as the main objection to the pituitary gland origin of this syndrome was the absence in many cases of any evidence that could be interpreted as pointing to a lesion of this gland, so the same objection holds to the Biedl and Raab hypothesis; no evidence of a high or massive dorsum sellæ has been found in many cases of the fully developed syndrome.

Ornsteen⁴ offers a more satisfactory explanation based upon the embryologic development of the hypothalamic region of the diencephalon. He holds that a genetic defect of the prosencephalon (forebrain) is responsible for the adiposogenital dystrophy, retinitis pigmentosa and mental deficiency (a cerebral genotypic unit character) and that the polydactylism, skull deformities, atresia ani and other occasional anomalies are present only through the accidental coupling of somatic genotypic unit characters.

Because of the occasional association of congenital (nerve) deafness with the Laurence-Biedl syndrome (Boenheim) and also because nerve deafness frequently acts as a mutual equivalent for retinitis pigmentosa in the hereditary transmission of the condition (Nettleship⁹) it would seem that the cases here recorded represent a variation of the Laurence-Biedl syndrome in which deafness takes the place of retinitis pigmentosa. One would be inclined, therefore, to seek the same embryologic explanation for both, namely, developmental failure due to a genetic defect of the prosencephalon. However, nerve deafness cannot be explained on the same basis as the optic atrophy with retinitis pigmentosa; the entire inner ear including the otocyst (anlage of the cochlea, the definitive organ of hearing, and the ganglion of the auditory nerve) take their origin in the hindbrain rather than the forebrain. Nevertheless, there seems to be more to the association than a coupling of somatic genotypic unit characters which is the explanation Ornsteen offers for the occurrence of unrelated anomalies in the Laurence-Biedl syndrome such as polydactylism and atresia ani. Nettleship,⁹ in a thorough study of retinitis pigmentosa from a hereditary standpoint stated that the commonest associated degeneracy occurring in subjects of retinitis pigmentosa is congenital deafness of various degrees. In another study¹⁰ he states that retinitis pigmentosa, progressive nerve deafness and feeble-mindedness or idiocy seem capable of acting as mutual equivalents or substitutes. In the state of our present knowledge, therefore, we must allow that nerve deafness cannot be explained embryologically as an equivalent for retinitis pigmentosa in the Laurence-Biedl syndrome but that further embryologic investigations may throw more light on the occurrence.

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REVIEWS.

THE FIVE-YEAR PROGRAM OF THE COMMITTEE ON THE COST OF MEDICAL CARE, ADOPTED FEBRUARY 13, 1928. PUBLICATIONS Nos. 1 to 12. Pp. 39. Washington, D. C.: The Committee on the Cost of Medical Care. Price, 25 cents to \$1.00.

ADMITTEDLY one of the most pressing problems of the practice of medicine in this country is the high cost of medical care for the middle classes. It was a wise prevision, then, to create this agency to study the problem in a comprehensive way over at least a 5-year period, while the personnel of the rather large committee ensures that the task will be well done. The support of the Carnegie Corporation, the Milbank Memorial Fund, the Russell Sage Foundation and the Twentieth Century Fund has made possible a minimum outlay of over \$250,000. Thus far the following topics have been reported on: The Extent of Illness and of Physical and Mental Defects Prevailing in the United States; A Survey of Statistical Data on Medical Facilities in the United States; Hospital Service for Patients of Moderate Means; Medical Care for 15,000 Workers and Their Families; A Survey of the Medical Facilities of Shelby County, Indiana: 1929; Capital Investment in Hospitals; Private Group Clinics; A Survey of the Medical Facilities of the City of Philadelphia: 1929; A Study of Physicians and Dentists in Detroit: 1929; A Survey of the Medical Facilities of San Joaquin County, California: 1929; The "Municipal Doctor" System in Rural Saskatchewan.

E. K.

EGYPT. THE HOME OF THE OCCULT SCIENCES, WITH SPECIAL REFERENCE TO IMHOTEP, THE MYSTERIOUS WISE MAN AND EGYPTIAN GOD OF MEDICINE. By T. GERALD GARRY, M.D., M.CH., M.A.O., M.B.E. Pp. 193. London: John Bale, Sons & Danielsson, Ltd., 1931. Price, 7/6d.

IMHOTEP, the Wazir of King Zoser of the 3d Dynasty, has of recent years received so much "publicity"—perhaps more than in an equal number of previous centuries—that he is in danger of acquiring the false values that often attend the spot light. While it is in no way implied that the excellent work of Sethe, Hurry, Dawson and others affords basis for exaggerating this apparent superman who was later deified and replaced Thoth as the chief

Egyptian God of Medicine, yet the present critical analysis by one who appears to be qualified for the task is as timely as it is interesting.

The chapters on magic and medicine among the ancient Egyptians in the same way present a healthy scepticism to those who are wont to find that recent scientific achievements are but rediscoveries of phenomena already known by the ancients.

As to Imhotep, himself, it seems clear that only by possible future discoveries, if at all, can it be decided whether he was of human origin later deified, possibly another name for Zoser himself, of divine origin or possibly that his name ("He who comes in peace") was merely an epithet of Ptah. He may still prove to be our earliest known physician or earliest God of Medicine; but as yet he can hardly be said, in Osler's phrase, "to be the first figure of a physician to stand out clearly from the mists of antiquity." Rather should we still agree with Hurry, "Nothing is known of his special work as a physician."

E. K.

THE GREAT PHYSICIAN. A LIFE OF SIR WILLIAM OSLER. By EDITH GITTINGS REID. Pp. 299; 10 illustrations. New York: Oxford University Press, 1931. Price, \$3.50.

THE continuing interest in this great humanist suggested that, in spite of the mass of biographic material that has been published in the past decade and of the masterly two volume *Life* by Harvey Cushing, a shorter story with more sweeping brush strokes would be desirable. Mrs. Reid consented to undertake the difficult task and the result shows the wisdom of the conception and of the choice of author.

With enough of the bare facts as a framework to carry a connected chronologic sequence of events, the author has built up a loving picture of the spirit of "a transcendently beautiful life." With a minimum of duplication of previously published biographic material, and with due regard for Osler's scientific achievements, she has painted a portrait that vibrates with life and must capture even future generations with its charm. The 18 pages of "The End"—already beautifully told by Cushing—will rank high as literature, while to those who loved her hero they raise emotions too poignant for contemplation unrelieved by action. Whatever the position in medical history assigned to Osler by posterity—and none would have been more careless of the result than the man himself—it will doubtless be largely determined by the beneficent interest in and influence exerted on his fellows. This tribute, then, should not only bring pleasure to many not yet acquainted with this "beloved physician," but should be valuable in preserving for

posterity the essence of an elusive spirit whose greatness might otherwise be more difficult to appreciate than that of lesser souls with perhaps more concrete achievements. E. K.

THE NOTE-BOOK OF EDWARD JENNER. With an Introduction on JENNER'S WORK as a Naturalist. By F. DAWTREY DREWITT, M.D. (OXON.), F.R.C.P., formerly on the Committee of the British Ornithologist's Union, and on the Council of the Zoölogical Society of London. Pp. 49; 1 illustration. New York: Oxford University Press, 1931. Price, \$1.25.

THIS manuscript note-book of the great vaccinator, covering the period 1787-1806, has been in the possession of the Royal College of Physicians since 1888, where it has evoked so much interest that it was thought desirable to make it available to a larger circle of readers. It throws an interesting light on Jenner's activities as a naturalist and comparative pathologist. The short but important notes on the habits of the cuckoo form the basis for his paper before the Royal Society on which his fame as a naturalist chiefly rests. The longer, industrious notes on hydatid cysts afford accurate and vivid descriptions, but served to support Jenner's erroneous belief, "long ago conceived" that hydatids were the cause of "true tuberculous consumption." The lack of microscopic aid is but too obvious. In the notes on dog's distemper, no definite conclusions were reached, and indeed could hardly have been expected at that time. E. K.

OXFORD MONOGRAPHS ON DIAGNOSIS AND TREATMENT. Edited by HENRY A. CHRISTIAN, M.D., Sc.D., LL.D., Hersey Professor of the Theory and Practice of Physic, Harvard University. Ten volumes. New York: Oxford University Press, 1928-1931. Price, \$100 set of 10 volumes. (The first 9 volumes, of which No. VII is still incomplete, appeared in the course of the last 3 years and have been reviewed in a previous issue of this Journal: 1931, 181, 270.) VOL. X. THE DIAGNOSIS AND TREATMENT OF PNEUMONIA. By CAMPBELL P. HOWARD, B.A., M.D., C.M., F.R.C.P. & S. (CAN.), Professor of Medicine, McGill University, and Physician to the Montreal General Hospital. Pp. 263.

THIS volume, which in the original prospectus of this set of books was entitled "Diagnosis and Treatment of Acute Respiratory Infections including Pneumonia," is apparently to be limited to a consideration of pneumonia. It is as yet incomplete: only lobar pneumonia has been covered, a section on bronchopneumonia is to

be issued later. While in the other volumes of the series diagnosis and treatment have received the major emphasis and space, the section on pneumonia has been written in the manner and scope of a "system" article. There are chapters on (1) History, Incidence and Etiology; (2) Infection and Immunity; (3) Morbid Anatomy; (4) Symptomatology; (5) Physical Signs; (6) Complications; (7) Clinical Types and Diagnosis; (8) Prognosis and Prophylaxis; (9) Treatment. The material is very well and for the most part adequately presented. Empyema, however, especially the management and differentiation of borderline cases, deserved a fuller discussion.

R. K.

THE CAUSATION OF CHRONIC GASTRO-DUODENAL ULCERS. A NEW THEORY. By J. JACQUES SPIRA, M.R.C.S. (ENG.), L.P.C.P. (LOND.). With an Introduction by SIR HUMPHRY ROLLESTON, BART., G.C.V.O., K.C.B., Regius Professor of Physic in the University of Cambridge. Pp. 78. New York: Oxford University Press, 1931. Price, \$2.50.

IN the introduction it is stated: "The thesis here presented is of considerable practical interest, for it incriminates a food factor as the responsible cause. . . . Stated briefly the argument is as follows: fat when introduced into the stomach regularly causes regurgitation of the duodenal contents, including bile, into the stomach; and bile-salts, when mixed with the acid gastric contents, damage the mucous membrane of the stomach." While the author gives much collateral material in support of his theory it is to be regretted that he gives so little evidence of his own. Under "experimental evidence" he offers no original observations, while the "clinical experience" offered is practically limited to 5 inadequate case reports and the statement that "for over a period of more than 10 years, a treatment based entirely on this conception of the disease has given me remarkably consistent and uniformly satisfactory results."

R. K.

MANUAL OF SURGERY. VOLUME I: GENERAL SURGERY. By ALEXANDER MILES, M.D., LL.D., F.R.C.S., Ed., Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S., Ed. and ENG., Professor of Surgery, University of Edinburgh. Pp. 574; 176 illustrations. Eighth edition. New York: Oxford University Press, 1931. Price, \$3.80.

THE eighth edition of this well-known surgery is marked by the addition of Mr. D. P. D. Wilkie to the editorial staff. In addition there have been some twenty of the younger men of the Edinburgh

faculty whose aid has been enlisted as "coadjutors in revision of the text." The revision has been thorough and has brought the text up to date in most respects. The previous arrangement of the material has been followed in the new edition. Excellent chapters on repair, inflammation, suppuration and ulceration are given. Surgical tuberculosis, syphilis and tumors are discussed in more detail than is usual in most American texts. The chapters on the various systems, as the bloodvessels, lymph vessels and glands, nerves, bones, etc., are preceded by short summaries on the anatomy and physiology of the tissue. The chapter on diseases of bones and joints is especially complete.

The book is simply and clearly written and fairly well illustrated. The therapeutic suggestions adhere somewhat to the older methods, but the work well represents the excellent teachings of the Edinburgh school.

L. F.

BEDSIDE INTERPRETATION OF LABORATORY FINDINGS. By MICHAEL G. WOHL, M.D., Associate Professor of Experimental Medical, Temple University Medical School. With an Introduction by JOSEPH MCFARLAND, M.D., Sc.D., Professor of Pathology, University of Pennsylvania. Pp. 321; 133 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$6.00.

THE author's preface emphasizes the fact that it is the purpose of this book to evaluate, rather than to describe in detail, those laboratory tests most used in present day diagnostic medicine. A few of the more widely accepted methods are described in detail, as one would find them in any physiologic chemistry, and other tests necessitating specialized laboratory technique are considered only from a clinical standpoint. The author experienced some of the natural difficulties in the selection of material for such a brief but comprehensive work; for example, he gives a rather extensive survey of parasitology and hematology, and quite sketchy discussions of dermatology and bacteriology. However, the real value of this work lies in its sound criticisms of the inaccuracies and errors in clinical interpretation of those laboratory procedures considered of greatest usefulness to the general practitioner.

S. S.

PRACTICAL ZOÖLOGY. By ROBERT W. HEGNER, PH.D., Professor of Protozoölogy, Johns Hopkins School of Hygiene and Public Health. Pp. 561; 332 illustrations. Revised edition. New York: The Macmillan Company, 1931. Price, \$1.80.

THIS is an elementary text-book of zoölogy intended for use in secondary schools, and material presented covers the entire animal

kingdom. Space, of course, is limited but the attempt has been made to present facts that will focus the attention of beginners on the more common representations of the various animal groups. The economic value of different groups of animals meets with special attention. The text is supplemented by numerous illustrations, references to readily accessible sources, a glossary and an index.

H. R.

BOOKS RECEIVED.

NEW BOOKS.

- Progressive Medicine*, Vol. IV, December, 1931. Edited by HOBART AMORY HARE, M.D., LL.D., assisted by LEIGHTON F. APPLEMAN, M.D. Pp. 456; 76 illustrations. Philadelphia: Lea & Febiger, 1931.
- Practical Endocrinology*. By HENRY R. HARROWER, M.D. Pp. 704. Glendale, Calif.: Pioneer Printing Company, 1931. Price, \$5.00.
- Conquering Arthritis*. By H. M. MARGOLIS, M.D. Pp. 192; 2 illustrations. New York: The Macmillan Company, 1931. Price, \$2.00.
- Osler and Other Papers*. By WILLIAM SYDNEY THAYER, M.D., LL.D., DR. HON. SC.D., F.R.C.P. IRE., HON., Professor Emeritus of Medicine at the Johns Hopkins University. Pp. 386. Price, \$3.50.
- Les Maladies de L'Esprit et Leurs Medecins. Du XVI^e au XIX^e Siècle*. By M. LAIGNEL-LAVASTINE and JEAN VINCHON. Pp. 377; illustrated. Paris: Norbert Maloine, 1930.
- Publications of the Committee on the Cost of Medical Care*. By various authors. For titles of the 12 pamphlets thus far published see review in this number of the JOURNAL. Washington: The Committee on the Cost of Medical Care, and Chicago: The University of Chicago Press, 1928-1931. Price for each publication: 25c to \$1.00.

NEW EDITIONS.

- Practical Morbid Histology*. By ROBERT DONALDSON, M.A., M.D., CH.B. (EDIN.), F.R.C.S.E., D.P.H., Sir William Dunn Professor of Pathology in the University of London, etc. With Foreword by SIR HUMPHRY ROLLESTON, BART. G.C.V.O., K.C.B., M.D., Regius Professor of Physics, University of Cambridge. Pp. 487; 214 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1931.
- Bacteriology for Nurses*. By HERBERT FOX, M.D., Director of the William Pepper Laboratory of Clinical Medicine in the University of Pennsylvania; Pathologist to the Zoölogical Society of Philadelphia, etc. Pp. 311; 91 engravings and 7 colored plates. Fifth edition thoroughly revised. Philadelphia: Lea & Febiger, 1931.

"With the opinion that it is now desirable for nurses to know more microbiology, the author has added a number of directions for the growth and study of bacteria, protozoa and metazoa, for the use of the microscope, skin tests, blood typing, etc. The subject is presented in an accurate, dignified manner. The illustrations are appropriate and well done."

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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AND

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Postvaccination Encephalitis.—Encephalitis following vaccination is a disease of unknown etiology that has been recognized only in the last seven years. Following the original observation of Lucksch, who reported 3 cases of nervous manifestations following vaccination that occurred in Czechoslovakia, some 600 other cases have been reported from Europe. ARMSTRONG (*Ann. Int. Med.*, 1931, 5, 333) says that in the United States 51 proven or probable cases have been recorded for the 10-year period just prior to 1931, 41 cases occurring in the last 3 years, a rough average of about 1 case for each 350,000 vaccine points sold in the United States during this time. These figures are probably not representative of the actual frequency of the disease in the United States. For example, 3 cases of encephalitis following vaccination have been admitted to the Charity Hospital, New Orleans, in the past 9 months. In Europe the large number of cases that were reported in 1926–1927 is a matter of record. The etiology of this type of encephalitis is not definitely known. French investigators believe that it is the vaccine virus directly which is implanted in the central nervous system to produce the disease. They have substantiated their contention by reasonably well-controlled experimental methods. The German students of encephalitis, on the contrary, lean toward the idea that the vaccine virus primarily is not the cause of the disease; rather that the encephalitis develops as a result of the presence of a virus, in a given community, which is of unknown origin and which is lying dormant, to become activated when the individual is vaccinated. The proof that the Germans have deduced does not seem to be as definite as that obtained by the French in support of their idea concerning the cause of the disease. Confirmatory evidence of the German idea might be obtained from one of the statements made in Armstrong's

paper, that the heaviest incidence in the United States occurred in a city of about 450,000 inhabitants. These cases were vaccinated by five different vaccinators, who employed different measures, but all of whom employed the same manufacturer's vaccine, but this same manufacturer distributed this lot of vaccine all over the United States and no other cases of encephalitis were reported. In the diagnosis of the condition there is one important feature which should be accentuated, and that is that the encephalitis symptoms develop almost invariably in from 10 to 14 days after vaccination. If the central nervous symptoms arrived 17 to 24 days after vaccination then the symptoms are probably due to postvaccination tetanus. The most important one single measure of prevention lies in the vaccination of children in the first year of life. Postvaccination encephalitis rarely occurs among infants vaccinated at this age period. Vaccinations performed in later life produce the great bulk of the cases of encephalitis following vaccination. In Europe it has been customary to employ multiple insertions in the technique of vaccination. The Rolleston Commission recommends a single small implantation of virus. It has also been suggested that dilutions of the virus be employed in vaccinating half-grown children and young adults rather than employing full-strength virus.

SURGERY

UNDER THE CHARGE OF
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Postoperative Pulmonary Atelectasis.—BROWN (*Arch. Surg.*, 1931, 22, 976) says that the importance of the bronchial secretions in producing postoperative atelectasis and in determining the specific type of atelectasis which ensues is stressed. Experimental and clinical observations are compared and are found to agree. Thick tenacious sputum is noted to plug the larger bronchi, whereas thinner sputum tends to greater dispersion and a blocking of the finer bronchi and bronchioles, thereby producing a scattered lobular atelectasis. The impression is gained that spinal anesthesia predisposes to postoperative pulmonary atelectasis.

Ollier's Disease—Unilateral Chondrodysplasia.—BROMER and JOHN (*Am. J. Roentgenol.*, 1931, 26, 428) believe that a review of the literature does not determine whether this disease, extremely disabling because of its unilateral retardation of bone growth, is an unusual manifestation of the condition known as hereditary deforming chondrodysplasia, as Keith, Stocks, Hale and others believe, or is a distinct entity, as Ollier and others have claimed. The fact that Cleveland's case was under observation for a sufficient length of time to show that the affected long bones are growing, and that the lesions are undergoing delayed

ossification and spontaneous healing, tends to support Ollier's theory. The 26 cases here collected are all similar and, as Cleveland stated in his summary, the clinical picture of each case is so like the others that even if there is no clear-cut pathologic differentiation from a much larger class of cartilaginous dystrophies, they seem to fall into a definite clinical group. A study of more patients from infancy to maturity and more experimental work such as that of Bentzon may ultimately be of assistance in answering the question as to whether or not Ollier's disease is a separate entity.

Varicose Ulcers.—WRIGHT (*Brit. Med. J.*, 1931, 3690, 561) says that varicose ulcers and their complications all result from loss of balance between arterial and venous systems of the leg. This balance can be restored in two ways, by lying down and by reinforcing the skin with an elastic support. In the cases due to varicose veins great improvement can be made by obliterating and in bad cases also ligating the varices, so that 75 per cent of ulcer cases can be cured and remain cured without any support but the elasticity of the patient's own skin. Ulcers of the leg will always be with us until we find a way of preventing femoral thrombosis after operations, fractures and childbirth, but they will diminish in number because of the simplicity of the injection treatment for early varicose veins. By this method of treatment there is a certain way of curing all gravitational ulcers. The larger ulcers, formerly acknowledged to be incurable, can now be readily cleared up by this method even when of the gigantic dimensions of 180 square inches ($1\frac{1}{4}$ square feet). The author holds that it is one of the most wonderful things in Nature to see the ulcer which may have started a quarter to a half century ago begin to throw up its granulations, flatten out its margins, pull in its edges and epithelialize in the way described so well by John Hunter many years ago.

Rapid High Temperature Deaths Following Biliary Tract Surgery.—CONNELL (*Ann. Surg.*, 1931, 94, 363) states that the fatal high temperature reaction following biliary tract surgery appears to be a definite clinical entity. Seventeen such cases occurring in 72 deaths after biliary tract operations are analyzed. It would seem rational to consider the syndrome as a metabolic, chemical or allergic reaction or to a nervous phenomenon, the exact nature of which is unknown. Instances of spontaneous recovery (what might be termed abortive) do occur but present no characteristic feature differentiating them from the fatal cases. Treatment in the absence of etiologic factors is symptomatic. Therapeutic efforts in the "abortive" cases fail to give a clue to effective treatment. A review of postoperative records in laparotomies for conditions other than biliary tract disease failed to show similar temperature reactions. Further study it is hoped will clear up the subject and develop an effective therapy.

Fascia Lata Grafts.—HORSLEY (*Ann. Surg.*, 1931, 94, 410) claims that dead alcohol-preserved fascia of an ox and living autogenous fascia react similarly in the peritoneal cavity and in the abdominal wall of the dog. In no instance does encapsulation occur. Kangaroo tendons soon become encapsulated and are absorbed more quickly in the

abdominal wall than in the peritoneal cavity. The fascias, both dead, alcohol preserved of the ox and the autogenous, atrophy and stretch when placed in the peritoneal cavity, but not in the abdominal wall. For pyloric occlusion chronicized kangaroo tendon is much more satisfactory, forming total occlusion for over 6 months in the dog and causing fewer adhesions than the fascia. The living fascia seems to occlude the pylorus several weeks longer than the dead alcohol-preserved fascia of the ox. If infection is present both the living and the dead alcohol-preserved fascia of the ox are broken down and absorbed, while chronicized kangaroo tendon shows a high degree of resistance to infections. The alcohol-preserved fascia of the ox does not react in man as it does in the dog, but is quickly absorbed and loses its tensile qualities, while the autogenous fascia lata in man apparently retains its strength.

THERAPEUTICS

UNDER THE CHARGE OF
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AND

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The Action of Digitalis on the Ventricular Portion of the Human Electrocardiogram.—WINTERITZ (*Ztschr. f. Krebsforsch.*, 1931, 33, 452) summarizes a carefully controlled series of investigations upon the effects of digitalis on the Q-R-S and T complexes of the electrocardiogram in some 500 patients. Of this group 143 proved available because their observations were free from all disturbing factors. In 13 per cent no influence upon the ventricular portion of the electrocardiogram was observed despite the definite presence of therapeutic or toxic action of the drug. Conversely, changes in the electrocardiogram were observed without any other evidence of digitalis action. The most frequent change in the electrocardiogram was an alteration in the amplitude of the waves, affecting either the initial complexes (Q-R-S) or the T wave. It was especially observed that the amplitude of the waves was increased by digitalis in those cases showing low voltage prior to treatment. This reversible low voltage is of prognostic significance as indicating the existence of a transitory myocardial impairment, and such cases as present it are to be distinguished sharply from those showing the irreversible form. In the present group one-half of the patients presented the more favorable reversible type of low voltage. The author calls attention to the fact that changes in the amplitude of the waves must be studied critically in order to eliminate those due to various extra cardiac factors, such as change in position of the heart, rotation of the electrical axis and the like, due to alterations in the position of the diaphragm, and changes due to variations in the accuracy of the application of the

electrodes. All of these factors were eliminated in the group of cases from which the author draws his conclusions. He points out, however, that the wide divergence of opinion observed in the literature may possibly be explained on the basis of neglect of the control of these factors. Depression of its amplitude or inversion of the *T* wave may be quite independent of the action of digitalis, as indicated by others, where it is due to one-sided ventricular preponderance. In such cases digitalis has the tendency to alter the *T* wave and the *S-T* line in the opposite direction to that of the initial complex, thus positive *T* waves are increased in their positiveness and negative waves become deeper. A depression of the *T* wave, therefore, is by no means a constant digitalis effect. This occurred in only 24 per cent of the cases, as a phenomenon independent of a preëxisting axis deviation, while digitalis exaggeration of the amplitude of the *T* wave which is dependent upon the direction of the initial complex occurred in 34 per cent of the cases. In these two groups toxic manifestations were present in 59 per cent of the first group and in only 37 per cent of the second. There was no instance observed among the 143 cases in which digitalis caused prolongation of the *Q-R-S*, while in 3 instances showing preëxisting prolongation digitalis led to some shortening of the time or to its return to normal. In 1 case right-sided bundle-branch block disappeared under the influence of digitalis. There is evidence for believing, therefore, that digitalis may improve intraventricular conduction. From all of his studies the writer suggests that digitalis tends toward restitution of that form of the electrocardiogram which was present in the given patient prior to the development of cardiac failure.

The Treatment of Migraine With Extract of the Anterior Lobe of the Pituitary.—It is a common observation that women suffering from frequent and severe attacks of migraine are often completely free from such attacks during pregnancy, only to have them begin again at the cessation of lactation. KLAUSNER-CRONHEIM (*Deutsch. med. Wchnschr.*, 1931, 57, 1455), acting upon this observation and the studies of Aschheim and Zondek, which showed the presence of large quantities of anterior lobe hormone in the blood of pregnant women, treated 10 patients by the oral administration of an active anterior lobe extract. All the patients were suffering from severe migraine of long standing and unrelieved by previous therapy. Of the 10 patients 7 were either entirely relieved or showed marked diminution in their pains while 3 were unaffected. Of the 7 patients in whom improvement or relief took place 1 was unable to continue the treatment because of the production of severe menstrual disturbance, while 2 more showed increase in menstruation and a shortening of the intermenstrual interval which, however, did not prevent the continuation of treatment. Investigation showed that in those patients successfully treated by this method there was no effect upon the elimination of sodium chloride indicating that the beneficial action was quite different from that following the restriction of chloride intake. The author believes that in these cases of migraine there is probably some toxic substance circulating in the blood which is fixed or destroyed by the anterior lobe hormone. Its failure to relieve certain patients suggests, however, that this is not always the case and leaves the question of the cause of migraine unexplained in these nonresponsive patients.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Calcium and Phosphorus Metabolism of Infants Receiving Undiluted Milk.—VAN KIRK (*Am. J. Dis. Child.*, 1931, 42, 1090) presents 70 observations of the calcium and the phosphorus intake, output and retention of a group of infants fed undiluted milk. The average daily retention of calcium ranged from 0.070 gm. per kilogram at 2 months to 0.044 gm. per kilogram at 10 months of age. The average daily retention of phosphorus ranged from 0.040 gm. per kilogram at 2 months to 0.027 gm. per kilogram at 10 months of age. The calcium-phosphorus retention ratio ranged from 1.3 to 2.3 with an average of 1.75:1. The average calcium content of the blood was 12 mg. per 100 cc. with 10 as the lowest value obtained and the average phosphorus content was 6.3 mg. per 1000 cc. with 5.4 as the lowest value observed. Measurements of calcified areas showed no widening of the distal end of the shaft of the radius and an excellent rate of ossification of the carpal centers. Roentgenograms of the wrists showed certain irregularities in the growth of bones frequently associated with mild rickets. Owing to the large amounts of calcium and phosphorus retained by these infants, the consistently high blood values, the excellent growth of the carpal centers, and the occurrence of the rachitic changes in summer as well as in winter, the question is raised whether these slight irregularities of growth at the epiphyseal junctions unaccompanied by rarefaction are rachitic or whether they may be normal accompaniments of the rapid increase in the rate of growth.

Undulant Fever in Children.—ANDERSON AND PÖHL (*Am. J. Dis. Child.*, 1931, 42, 1103) state that many authors in describing undulant fever of bovine origin have mentioned the slow, poorly defined, insidious character of the onset. Weakness, anorexia, fever, chills and profuse sweats are usually the prominent symptoms as the disease becomes established. Subacute migrating pains in the extremities, joints, back and muscles, and headache are mentioned. The physical examination elicits no characteristic signs. A roseolar, macular, scaling eruption has been observed in a few cases. Loss of weight, abdominal tenderness, enlarged spleen, slight anemia and slight leukopenia are found in a variable number of cases, with continued fever the only consistent feature. The disease runs a variable course from weeks to years, averages about 3 months, and gradually subsides, usually without serious sequelæ. In none of the 3 cases, the subject of this report, was it possible to make a definite clinical diagnosis of undulant fever. The physical findings were exceedingly irregular and largely negative, but the persistent fever prompted the submission of blood specimens for agglutination tests. In each case it was possible to trace the infection to the cows supplying the milk which these children habitually used. These 3 cases all ran short courses of from 7 weeks to 8 months. The children were at no time seriously ill, and apparently all recovered

without complication or sequelæ. Typical undulation of fever was not observed. There were periods of high fever which followed exertion, but the fever subsided after rest.

Nutritional Edema.—WEECH and LING (*J. Clin. Invest.*, 1931, 10, 869) consider the serum protein deficiency in relation to various types of edema, both experimental and clinical. They call attention to other factors and in particular to the rôle of several inorganic salts in modifying the effect of protein deficiency alone. In a series of patients suffering from nutritional edema, who were studied during both the active and the convalescent stages, it was found that when the level of serum albumin was greater than 2.9 gm. per 100 cc. edema was never observed, and that when the level fell below 2.5 gm. per 100 cc. edema was invariably present. The correlation with total serum protein, although not so close, was sufficient to indicate a critical level for edema close to 5 gm. per 100 cc. Serum globulin was exceedingly variable as decreased, normal and increased values were all found in association with edema. Decreased globulin generally occurred only when the albumin was also decreased and this was usually present in association with edema. No relation of cause and effect was considered to exist between lowered globulin and edema. The results of metabolism observations were noted on 2 of these patients. In both cases the combined administration of sodium chlorid and sodium bicarbonate led to rapid gain in weight with marked increase in edema and depression of chlorid excretion in the urine. In one of these cases these effects could not be duplicated, after feeding an adequate diet had resulted in a return to normal of the serum protein. It is pointed out that it is impossible to offer an exact explanation of all the effects observed, although it is indicated that the results are in harmony with the view that the cation sodium is more intimately related with the causation of edema than the anion chlorid.

The Effect of Large Doses of Irradiated Ergosterol on Nitrogen, Calcium and Phosphorus Metabolism in Rats.—KERN, MONTGOMERY and STILL (*J. Biol. Chem.*, 1931, 93, 365) found macroscopic and microscopic evidence of the accumulation of much calcium in the kidneys in growing rats receiving large daily doses of viosterol. Chemical analyses of those organs revealed the deposition of calcium to be much greater in females than in males. Viosterol in larger doses increases the absorption of calcium from the intestine. The excretion of calcium in the feces decreases and the excretion in the urine is greatly increased. To a lesser degree there is also a diminished fecal elimination of phosphorus. Ergosterol irradiated in alcohol produces greater disturbance of the calcium metabolism of growing rats than ergosterol either irradiated in ether or irradiated dry, on the basis both of actual weight of ergosterol fed and of the vitamin D content of the samples. It is believed that the medium in which the ergosterol is irradiated plays an important part in the development of toxicity. The nitrogen excreted in the urine seemed to have been entirely within the normal range, being affected mainly by the level of food intake. Whatever changes may occur in the way of deposition or absorption of bone in rats fed large amounts of viosterol, analyses of the leg bones of these animals show normal content of calcium, phosphorus and carbon dioxide.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Amebiasis Cutis.—ENGSMAN and MELENEY (*Arch. Derm. and Syph.*, 1931, 24, 1) reëmphasize the fact that ulceration of the skin may at times be due to an ameba in some cases identified as *Endameba histolytica*. The cases reported fall into four groups: (1) Those following the drainage of an amebic abscess of the liver; (2) those following the drainage of a lesion of the appendix or other areas of the lower portion of the intestine; (3) those about the anus associated with amebic colitis; and (4) those without any direct connection with the viscera. The authors in describing the clinical picture of amebic ulcers, particularly stress the rapidity of spread of the ulcerative process, the overhanging edge from under which pus can be expressed, and the surrounding erythematous terrain. Usually motile amebæ can be identified in fresh preparations from the ulcers but at times are discoverable only in fixed smears and sections. Emetine hydrochlorid is the accepted method of treatment.

Sensitizations.—SULZBERGER and MAYER (*Arch. Derm. and Syph.*, 1931, 24, 537) contribute a timely article on the discrepancies in results obtained by an attempt to duplicate previous experimental work and point out that the factor of geographical localization of the experiments performed has never been given sufficient weight in the analysis of the data involved. The authors believe that differences in the race, feeding and housing of the test subject or experimental animals are factors which may entirely alter results obtained by similar methods at widely separated points. They have observed, for example, that guinea-pigs reacted differently when sensitizations with the same brand of neoarsphenamine were attempted in Breslau, Zurich and New York, the results varying from 98 per cent successful sensitizations in Breslau to none in New York. These differences were constant in spite of experiments carried out with care to provide for identical technique. A study of the modifying factors disclosed among other things that the diet of the experimental animals was of decided importance, green fodder inhibiting and dry fodder favoring sensitization. The authors wisely counsel that the knowledge and consideration of these facts may alter premature decisions on contradictory experimental results and account in part for differences in clinical, epidemiological and seasonal fluctuations noted under varying environment.

GYNECOLOGY AND OBSTETRICS

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Carcinoma of the Cervical Stump.—Those who favor the performance of total hysterectomy as a routine base their preference on the fear of the later development of cancer in the retained stump of the cervix which is left after the supravaginal operation. Various estimates have been made as to the frequency of this condition but on account of the comparatively small number of cases which are seen in any one clinic it is difficult to arrive at a representative figure. This subject has been investigated by MAYO and MAYO (*Ann. Surg.*, 1931, 93, 1215) who studied the records of 99 patients with cancer of the retained cervix who had been seen in the Mayo Clinic during the preceding 20 years. A larger number of cases was found within the first 2 consecutive years after subtotal hysterectomy than in any 2 years thereafter, although more than 50 per cent occur 3 years or more after subtotal hysterectomy. The condition must be considered serious because ultimately so few patients are cured, perhaps because the disease is not diagnosed until it is far advanced. They feel that at the primary operation the total hysterectomy should be the operation of choice since they can show a mortality of 1.8 per cent for this operation as against 1.2 per cent for the subtotal hysterectomy in two series large enough to be of importance. If the surgeon fears to perform the total operation but nevertheless believes that the retained cervix may be a future menace to the patient, they advise the performance of the subtotal operation, followed in 10 or 12 days by some method of removal of the cervix, such as enucleation of the canal or destruction of the cervical canal by cautery. While their argument seems rather convincing, nevertheless their figures show that in spite of the wealth of material at their disposal with consequent extensive experience, the total operation has a higher mortality in their hands as in the hands of nearly every other gynecologist or surgeon.

Renal Irradiation for Ureteral Fistula.—When in the course of a pelvic operation the ureter has been injured and the damage recognized at once, the operator must quickly decide as to what measures must be taken to alleviate the injury. The ideal policy when possible is to perform immediate anastomosis of the cut ends or to transplant the upper end into the bladder, while some operators are content to merely ligate the ureter in order to cause atrophy of the corresponding kidney. Many ureteral injuries however, are not recognized until several days after the operation, when a leakage of urine from the vagina

reminds the gynecologist that all is not well. Under such conditions a secondary operation may be quite a hazardous procedure and for this reason the suggestion was made several years ago that the easy and safe method of handling such a situation was to irradiate the kidney of the affected side with sufficient dosage to cause its atrophy and thus a bloodless cure could be obtained. As a result of his experiences with this procedure Otto (*Zentralbl. f. Gynec.*, 1931, 55, 1529) concludes that irradiation of the kidney should only be considered as a means of treatment when the function of that kidney is largely destroyed providing, of course, that the functional capacity of the opposite kidney is good. In such cases good results may be looked for. When the kidney corresponding to the injured ureter has good function he believes that it is much more desirable to implant the ureter into the bladder or bowel since irradiation will frequently fail to cause atrophy of normal renal tissue.

OPHTHALMOLOGY

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Extraocular Muscle Paralysis Following Spinal Anesthesia.—FAWCETT (*Minnesota Med.*, 1931, 14, 648) reports 2 cases of external rectus paralysis following spinal anesthesia with novocain. In the first patient the paralysis developed on the thirteenth day postoperative and cleared up completely in 13 days. In the second patient the paralysis developed on the twelfth day postoperative and was still present at the end of 17 months. This complication of the spinal anesthesia is relatively rare. Reber reports 5 cases in a series of 2000 anesthetics. The external rectus is the muscle most frequently involved. In 88 cases reviewed by Blatt the fourth never was involved in 4, the third in 6 and the sixth in 78. The interval between the anesthesia and the onset of the paralysis varies between 3 days and 3 weeks. The prognosis is favorable. In most cases the paralysis disappears in from 1 to 3 weeks. In a few it persists longer. The onset is usually accompanied by photophobia, headaches and dizziness. The etiology of the paralysis is still a matter of conjecture. It seems most probable that they are caused by an elective toxic action of the injected drug. However, they may have their basis in a mild localized meningitis or a localized hemorrhage. Van Lier has demonstrated swelling of the nuclei of the ganglion cells after spinal anesthesia. It is known that the injected drug often diffuses up around the medulla and base of the brain in appreciable concentration. So it is possible that the ocular muscle paralyses are due to degeneration of the ganglion cells.

Hereditary Optic Atrophy (Leber's Disease).—KUHN (*Arch. Ophthalm.* 1931, 5, 408) reports a case of hereditary optic atrophy (Leber's disease) in which an exploratory operation was performed on the chiasmal region. The patient was a man, aged 25 years, who complained of a sudden loss of vision first in the left and later in the right eye. Vision in the right eye was 20/100 and in the left the ability to count fingers at 12 inches. Perimetric studies revealed central scotomata, relative in the right eye and absolute in the left. The scotomata involved the temporal more than the nasal part of the fixation area. Ophthalmoscopic examination revealed bilateral mild optic neuritis with commencing atrophy in the left eye. General physical, laboratory and neurologic examinations were all negative. The sella was small and partially bridged. There was a definite familial history of sudden loss of central vision. An elder brother had relative scotomata and two maternal uncles had been similarly affected. Exploration of the chiasmal region showed no lesion except a mild arachnoiditis. However, the vision improved gradually, and three months after operation was 20/50 in the right eye and 9/200 in the left. Two months later the vision in the right eye fell to 20/200. Encephalograms and ventriculograms made at this time failed to reveal any pathologic condition near the optic chiasm but did suggest a chronic encephalomyelitis with some obstruction in the region of the fourth ventricle but without internal hydrocephalus. Seven months after the first operation the vision of the right eye was 9/200 and that of the left eye 8/200.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The So-called Bursa Pharyngea in Man: Its Origin, Relationship With the Adjoining Nasopharyngeal Structures and Pathology.—Plenty of proof of the correctness of Pasteur's aphorism—"in the fields of observation chance only favors the mind which is prepared"—can be found in such happy coincidences as Galileo and the swinging lamp in Pisa's cathedral; Newton and the falling apple; Jenner and the milk-maid's cowpox; Darwin and the Beagle's cruise; Beaumont and Alexis St. Martin's gastric fistula. Assisted by Meyers and Shirazy, DORRANCE (*Arch. Otolaryngology*, 1931, 13, 187), taking advantage of an unusual opportunity for detailed study of a bursa pharyngea in an adult with cleft palate, presents an exhaustive account of developmental, anatomic and clinicopathologic of pharyngeal bursa. Evidence is produced to show that the true bursa pharyngea, as encountered in adults, represents the persistence of the embryonal bursa and is to be looked upon as an independent structure which, although in intimate relationship with a coexistent adenoid, is not to be regarded simply as a medium recess of the pharyngeal tonsil or as necessarily bearing any relation to cleft palate. Its anatomic position is characteristic—in

the midline of the pharynx just anterior to the upper border of the superior constrictor muscle. Clinically, the bursa pharyngea is of interest. Forty-five years ago Dantzig's Tornwaldt called attention to certain inflammatory processes of the bursa associated with systemic disturbances. As Dorrance says, "When his opinion is considered in the light of modern medicine one finds that in spite of errors due to overenthusiasm he was anticipating the era of focal infection." In any event Tornwaldt's work stimulated in a neglected anatomic field and emphasized the embryologic complexity and clinical importance of the nasopharynx.

An Aural Syndrome of Hepatic Origin.—To Louis we owe largely the demonstration of the "numerical method" as a valuable instrument of investigation. The guiding motto of his life was "'Ars medica tota in observationibus'"—in carefully observing facts, carefully collating them, carefully analyzing them." Accurately to get knowledge of any disease it is necessary to study a large series of cases and to go into all particulars. A correlation of the occurrence of any one of these with all of the other data may reveal something of causal significance or diagnostic importance. Accordingly, from the mass of information acquire by a thorough and comprehensive survey in a large diagnostic clinic primarily designed to study diseases of the ductless glands, DRURY (*Ann. Otol., Rhinol. and Laryngol.*, 1931, 40, 415) has expiscated a series of 120 cases exhibiting ear involvement associated with hepatic dysfunction. The syndrome includes, in their order of frequency, such symptoms as deafness, tinnitus, vertiginous symptoms, headaches, fatigue and nausea. A characteristic audiometric finding is mentioned. The writer believes the syndrome to be due primarily to a long-standing toxemia of hepatic origin. Clinical improvement follows proper care and treatment.

RADIOLOGY

UNDER THE CHARGE OF

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Coccidioidal Granuloma: Roentgen Diagnosis.—This disease, which attacks lungs, bones and soft tissues, and pathologically, clinically and roentgenologically resembles tuberculosis closely, deserves the systematic and complete review given by CARTER (*Am. J. Roentgen. and Rad. Therap.*, 1931, 25, 715). The first case was reported from Buenos Aires in 1892; the second and third cases from California in 1894. In this country, approximately 80 per cent of all cases reported were Californian in origin, but scattered cases have been noted from Washington, Arizona, New Mexico, Colorado, Kansas, Nebraska, Missouri, Illinois, South Carolina and Pennsylvania. It is suspected that many cases go unrecognized. The disease is produced by a specific

fungus, oïdium coccidioides, which in its adult form is a spherule 15 to 40 microns in diameter, and which multiplies by endosporulation. Infection, it is believed, may occur through the abraded skin, through the alimentary canal and through the respiratory tract. Pulmonary invasion is considered to be most frequent. Pathologically characteristic of the disease is the production of submiliary, miliary or larger nodules which resemble tubercles. The nodules may caseate and subsequently liquefy or they may suppurate from the beginning. The lesions are nearly always progressive, but may heal eventually. Abscesses may occur in the soft tissues; lymph nodes tend to be involved early. In the lungs may be found extensive miliary lesions, nodular consolidations with caseation, abscesses or massive consolidations. The lesions of bone are essentially those of a destructive osteomyelitis. The clinical manifestations vary with the mode of infection and the situation of metastatic lesions. Frequently the onset is respiratory, with fever, cough and malaise. The disease may run a rapid course with early death. If the pulmonary symptoms subside or the primary infection is in the skin, the disease may become chronic for weeks, months or years. Positive diagnosis rests on finding the specific organism; a long search may be necessary. Treatment is unsatisfactory. Colloidal copper has given good results in a few cases. From the roentgenologic standpoint Carter has surveyed 50 cases. Ninety-four lesions were found in bone. They arose mostly in the region of cancellous bone and the process was predominantly destructive, although in a minority of instances bone production was noted. Adjacent joints were involved in only 28 cases. This seems to afford a mark of distinction from tuberculosis, in which the joint tends to be involved early. Sites and bones commonly invaded included the ribs, the malleoli of the tibia and fibula, tarsus, tuberosity of the tibia, the ulna, scapula, clavicle, patella, etc. Lesions arising in malleoli and other bony prominences seem to be rather suggestive of coccidioidal granuloma. The chest was examined in 37 cases and was involved in all but one. Miliary lesions were evident in 19; they were usually general and with localized accentuations in some portion of the lung, most frequently on the right side. Hilar thickening was evident in 31 cases and a definite mediastinal mass in 17. Parenchymatous infiltration distinct from miliary dissemination, was present in 32 cases, or 90 per cent; it varied from slight clouding to dense consolidation. Pleural involvement with effusion occurred in some cases. Compared with tuberculosis, the outstanding features of pulmonary coccidiosis are the high incidence of mediastinal involvement, miliary lesions and hilar thickening, the less fibrosis and cavitation, and the general softness and vagueness of the shadows. The advanced lesions resemble the caseous or pneumonic type of tuberculosis, but with less tendency to cavitation.

Radiation Therapy in the Treatment of Cancer of the Mouth and Lips.—MARTIN (*Radiology*, 1931, 16, 881) has had satisfactory results from radiotherapy by both radium and Roentgen ray. In his series there were 108 cases without evidence of metastasis at the time of treatment. Later 4 cases developed malignant nodes in the neck and died. The remaining 104 cases were well after 5 years. Eleven cases had definite involvement of lymph nodes when treatment was begun; all these patients died from cancer.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Successful Socialization and Compensation in Manic-depressive Psychosis.—HINSIE (*The Psychiatric Quarterly*, 1931, 5, 2, 312) remarks that with the advent of Freudian psychoanalysis, patients began to understand many of the causal relationships between their symptoms and the "buried complexes" allied to the instinctive realm—that it was observed that there was a series of closely identified relationships of psychical factors extending from consciousness deep into the unconscious field. Insight of this nature is decidedly apart from the insight that enables the patient to appreciate his mental phenomena only in terms of "morbid" or "normal." The former might be referred to as primary and the latter as secondary insight. When secondary insight is well developed and especially when it is supported by a desire on the part of the patient to expand the insight to the primary degree, psychotherapy may accomplish meritorious results. Further, the author remarks that it is a well established observation that subjects with a manic-depressive psychosis achieve periods of remission during which their "morbid" manifestations are relegated to the background. These individuals in the phase of remission, attain certain grades of social integrity, but there is not the psychological harmony that insures future integration at the higher levels. Relapses occur with much frequency. The manic-depressive patient is not altogether unlike the schizophrenic patient who exhibits periodically in his mental disorders. In both instances, there is more or less complete return to the pre-psychotic level. And, states the author, adjustment and integration are closely associated. When an individual coördinates his several capacities (physical, physicochemical, sensori-motor, psychologic and social), in the direction of a reasonable goal, and at the same time temporarily subordinates other issues, it may be said that that individual is well adjusted. The 6 cases presented were under active treatment and management for about 2 years and for about 5 years, they were not interviewed. As a result of the instituted work upon the patients, it was found that some of the patients responded very favorably. Others were appreciably assisted to adjust at a higher level than that to which they had formerly adapted themselves. There was a third group that was not at all benefited. This latter group consisted of patients that refused treatment of any nature. In addition, the author felt that in most cases the question of socialization and compensation is a question also of the socialization and compensation of his environment. An individual's career is made up not only of his own instinctive cravings, but also of the cravings of others. The individual's reactions are a resultant of instinctive processes, not only of those arising

ing within himself, but also of those that come to him from without. Hence, when socialization and compensation are under consideration, one must inevitably take into account the patient and several personalities that he has incorporated within himself. This implies a clear understanding of the emotional streams as they converge from several angles upon the subject under treatment.

Radiothermic Treatment of General Paralysis.—HINSIE and CARPENTER (*Psychiatric Quarterly*, 1931, 5, 2, 215) present a preliminary report of their findings in the radiothermic treatment of 17 cases of general paralysis. Eleven of these cases have left the hospital definitely improved, 5 are still in the hospital, having but recently completed their treatment, and 1 case is dead, having died shortly after the course of treatment started. The plan of approach was to produce the temperature curves of inoculated malaria in a series of patients with general paralysis. If these conditions were met, it was considered that there might then be more or less suitable control material by which the efficacy of radiothermic treatment might be computed. All patients were adults. Each was given treatment consisting of 70 hours of temperature. They noted the following facts: (1) The treatment was tolerated well; (2) the agent that induces the temperature rise is under immediate control; (3) the temperature rise may be gauged to meet the cardiovascular-nephritic capacity of the patient; (4) the patients usually show improvement while they are undergoing treatment; (5) there is a loss of 5 to 10 pounds of weight, which is promptly regained upon termination of the treatment; (6) there is a mild anemia, a reduction of hemoglobin, an increase of the polymorphonuclear cells, and the spinal cell count is reduced during the treatment—all swinging within normal limits upon termination of the treatments; (7) the blood solids and chlorids all remain within normal limits during the therapy; (8) the blood sugar tends to rise slightly during the radiothermic course. Concerning the Wassermann findings in the blood and spinal fluid, the authors make no note—stating that it is too early to form any opinion as yet, concerning this phase of their work.

Mental Factors that Affect School Abilities.—LINE (*Ment. Hyg.*, 1931, 15, 2, 255), remarks that present day educational research is showing the very marked and healthy influence of the mental hygiene movement. The genetic picture of childhood is being made more meaningful, more complete, because of the growing realization that a thorough understanding of that picture is necessary to a preventive program; and the influence of the school on the mental growth of the child is the particular emphasis now being made by those who are endeavoring to integrate educational research into the mental hygiene program. It is universally agreed that the genetic method is the one that is most ideal in arriving at the necessary foundation for a mental hygiene program. The case study method is a second best, or is a means whereby the genetic picture may be more immediately clarified for present guidance. He asks if we do not select our categories of observation largely—sometimes entirely—in terms of behavior, rather than in terms of psychologic (functional), manifestations; or if we do not sadly confuse our behavior concepts with the more subtle concepts of mental hygiene. He then states that there is a distinct differ-

ence in the implications of the two classes: that one really intends to refer only to descriptive aspects of behavior, to incidents that are observable by others; the second goes much deeper, and implies the functional picture. And by confusing this distinction, our conception of the genetic method tends to become that of a series of quantitative records. But in essence, the genetic method is undoubtedly qualitative, and must ultimately arrive at a qualitative interpretation of the cross-sectional picture of the child as he now is—a picture that can, of course, be meaningful only insofar as its antecedents and functional consequents are known. The evaluation of educational progress is ultimately qualitative, in the sense that a child is rated as superior or inferior to another in respect to a given "ability" or "trait." The basis of determining that rating may be more or less "objective," and may involve mathematical quantities, but fundamentally the entity postulated and measured, is an inherent mental quality or aspect. The qualitative correlation of educational abilities can be made to some extent in a more scientific way than is the case with behavior categories. The author asks whether one might not expect that an analysis of causes of success or failure in certain broad lines of activity would reveal other, more subtle, psychologic deviations, which have been overlooked in our training programs, and which have played a vital part in the genesis of special disabilities. And it is in this connection that one of Spearman's leads seems to have a significant application. After a completely satisfying objective demonstration of the general nature of intelligence, certain other functional unities are isolated. Spearman, after an interpretative supplement, puts forward the tentative hypothesis of "mental energy" to account for intelligence; but this energy displays marked individual differences, not only in quantity, but also in quality. The variation in "inertia" corresponds to the statistically demonstrable factor of "perserverations;" and differences in terms of fatigue recuperation manifest themselves, during continuous and concentrated mental work, as a greater or less oscillation or fluctuation in efficiency. These additional variables make the psychological analysis of a child much more meaningful and scientific than before; and the relationship between deviations along the new axis thus demonstrated and mental functioning in the classroom would seem to be worthy of investigation.

PATHOLOGY AND BACTERIOLOGY

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The Endocarditic Process (Valvulitis) in Childhood.—DE VECCHI (*Arch. Path.*, 1931, 12, 49) reports his findings from a careful histologic analysis of the heart valves of 42 children. Postmortem diagnosis of this condition is usually based on the macroscopic appearance of the valves. Such evidence, however, is fallacious as valves that are healthy

to the naked eye may show microscopic changes that are inflammatory in nature. This is especially true in the case of infants as the valvular apparatus is very delicate and the initial changes are difficult to detect. The lesions observed in areas macroscopically healthy consisted of desquamation of the valvular endothelium, sometimes with hyalinization and necrosis of the adjoining valvular tissue, accompanied by a lymphocytic infiltration of the deeper layers and a histiocytic reaction in the subendothelial layers. The histiocytic reaction was usually well marked and was not necessarily accompanied by endothelial desquamation. The essential nature of the endocarditic process is partly degenerative and partly inflammatory. The formation of thrombotic vegetations, he considered, is a secondary phenomenon which may be entirely absent, but he did not give much attention to disturbances in capillary circulation as affecting the local resistance and the deeper histiocytic reaction. The inflammatory reaction in the initial stages of the process he found to be always of the same type, whatever the stimulus, bacterial or toxic. In the later stages it varies with the nature of the micro-organism and the "resistance" of the subject. The inflammatory processes that develop in the valves of young children affected by various toxic infective diseases, he emphasized, are of particular importance, as their further development may give rise to the establishment of valvular defects, the mode of origin of which has hitherto been obscure.

Hemolytic Streptococci in Scarlet Fever and Epidemic Septic Sore Throat.—HERZBERG (*Monatschr. f. Kinderh.*, 1929, 43, 328) studied some 2200 throat swabs taken at monthly intervals from 170 inmates of a children's hospital and tuberculosis clinic for the presence of hemolytic streptococcus. The average findings of hemolytic streptococci were for children (2 to 15 years) 40 per cent, for those of the tuberculosis clinic 60 to 70 per cent, for infants 10 to 15 per cent. Single swabs from 150 inmates of a tuberculosis sanitarium taken in January gave 75 per cent and from 100 school children in July gave 17 per cent positive for hemolytic streptococci. The positive findings increased as a rule in the damp and cold months from September to December, but this was not constant. Twenty-six clinical cases of scarlet fever in the children's hospital comprised 17 from the tuberculosis clinic, 8 in age group 2 to 15 years, and 1 infant. He found no relationship between the incidence of hemolytic streptococci and the occurrence of scarlet fever, and concludes that none exists. No record is given that the strains of hemolytic streptococci were tested for toxin production by means of toxin-antitoxin injections. This study would have been more valuable if such toxin determinations had been done although the specificity of the toxin of scarlet fever strains is discounted by the work of WHEELER (*J. Preven. Med.*, 1931, 3, 181) who asserted that "it is impossible by the methods now available to separate the streptococci associated with epidemic septic sore throat and scarlet fever into definite groups which bear a specific relation to the particular type of infection induced." In one outbreak of streptococcus infection typical strains of *Streptococcus epidemicus* identical in all their reactions, including skin antitoxin tests, were isolated from the milk of one cow, from the throats of patients with septic sore throat and also from the throats of scarlet fever patients.

HYGIENE AND PUBLIC HEALTH

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Antigenic Value of Scarlet Fever Streptococcus Toxin Modified by the Action of Formalin.—VELDEE (*U. S. Pub. Health Rep.*, 1931, 46, 693) notes that various authors have reported on the successful use of scarlet fever toxin in the prevention of that disease. He also points out the disadvantages of the methods in general use following in the footsteps of Ramon who has prepared a harmless yet potent immunizing agent against diphtheria. Several workers have used formalin to produce an analogous product for scarlet fever. The author's own work has shown that a very high percentage of immune persons can be secured by the use of three doses of his toxoid, whereas five doses of unmodified toxin are required to bring about a similar result. The unpleasant reactions are much fewer when toxoid is used than when the unmodified toxin is employed.

Experimental Addiction of Animals to Opiates.—KOLB and DuMEZ (*U. S. Pub. Health Rep.*, 1931, 46, 698) present the results of an extensive series of studies on monkeys in which attempts to induce addiction by the use of morphin, codein and heroin were made. Monkeys were killed by subcutaneous injections of morphin sulphate as low as 85 mg. per kilo of body weight, and very severe symptoms with sickness lasting several days were caused by smaller doses, but 1 animal survived 125 mg. per kilo, and the minimum fatal dose was not accurately determined. Young and small monkeys survived larger doses per kilo than older and larger animals. Seven milligrams of heroin per kilo of body weight killed the majority of monkeys that had not previously been given a toxic dose. Some that had previously received a toxic dose of an opiate survived 8 mg. per kilo. Some monkeys that survived a toxic dose of morphin, heroin or codein were less severely affected by slightly larger doses given from a week to a month afterward. No monkey survived as much as 80 mg. of codein phosphate per kilo of body weight, and 1 died from 60 mg. per kilo. Codein caused convulsions frequently, heroin much less often and morphin never. By daily administration of morphin, heroin and codein monkeys were made tolerant of increasingly large doses. After 8 or 9 months 200 mg. per day of morphin caused less severe immediate symptoms than 10 to 40 mg. did during the first six weeks; 39 mg. of heroin caused less severe symptoms than did 4 mg. at first; 110 mg. of codein caused less severe symptoms than did 10 mg. in the beginning. One animal that

was started on morphin was kept on it or on heroin for 52 months. Gradual deterioration in general health was caused by daily administration of codein, morphin and heroin. Codein was decidedly the most harmful and heroin the least. Morphin caused marked dependence, shown by a crouching posture, facial distortion, hypersensitiveness, fall in temperature and, in 1 case, death on withdrawal of the drug. Heroin caused less dependence and codein was not definitely shown to produce dependence. Monkeys made tolerant to large doses of morphin, heroin or codein were tolerant to large doses of all three drugs, but the dependence produced by morphin and heroin was not satisfied by codein. Tolerance was almost completely lost in about 2 weeks after withdrawal of the drugs, and the monkeys improved in health and general appearance during the remainder of the period of abstinence. Monkeys abstinent for 6 weeks or 2 months after having received daily doses of morphin or heroin for 16 months or more were more sensitive and less resistant to the drugs when injections were started again than they had been in the beginning. Some of these cases reacted with marked spasticity.

PHYSIOLOGY

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Anesthesia in Ameba.—L. V. HEILBRUNN (from the Laboratory of Zoölogy, University of Pennsylvania). In many respects, the common ameba is an excellent form for the study of anesthesia. Because of its continuous movement, it is easy to establish criteria of anesthetic action. Moreover, the viscosity of the ameba protoplasm can readily be studied, and one can thus obtain information regarding the effects of anesthetics on the colloidal properties of the living substance. By studying the two common types of ameba, *Ameba dubia* and *Ameba proteus*, it is possible to study the physical properties both of the internal protoplasm and of the outer cortex or plasmagel. In *Ameba dubia*, it is a simple matter to determine the viscosity of the internal protoplasm (plasmasol) by the centrifuge method (Heilbrunn, 1929). On the other hand, when *Ameba proteus* is centrifuged, one may determine the speed with which granules or crystals are moved through the plasmagel. A complete picture of both the internal and the external protoplasm is thus obtained.

Ameba is readily anesthetized by potassium salts in dilute solution, and the potassium ion has a very marked liquefying action on the plasmagel. Magnesium has a less pronounced anesthetic action, and its effect on the plasmagel is less pronounced. The anesthetic action of both potassium and magnesium ions is antagonized by calcium. Preliminary studies with fat solvents indicate that in this type of anesthesia also, the plasmagel becomes more fluid. Certain other agents also stop the movement of the ameba by liquefying the plasmagel. These agents include heat and ultraviolet radiation.

The Reducing Power of Glomerular Urine and Blood Plasma from the Frog.—A. M. WALKER, J. R. REISINGER, and E. H. ELLINWOOD (from the Laboratory of Pharmacology, University of Pennsylvania). A micro modification of Sumner's dinitrosalicylic acid method was described which makes it possible to analyze 0.2 c.mm. of known glucose solutions with a maximum error of 3 mg. per 100 cc. The method is applicable to similar amounts of frog plasma, the results being in close agreement with those yielded by the Hagedorn-Jensen method. Thirty-two experiments have been completed on intact frogs in which the reducing substance content of glomerular urine and plasma have been measured. The mean difference between the two fluids was 2.1 mg. per 100 cc. with a mean deviation of 3. It was concluded that the reducing substance content of the two fluids is identical—a result in harmony with previous experiments from this laboratory which have indicated the function of the glomerulus to be one of filtration.

A series of 5 frogs received preliminary injections of phloridzin before the glomerular collections were made. In no one of these instances did the glomerular fluid contain more reducing substances than the plasma. It was therefore concluded that the glomeruli played no active part in the glycosuria which followed the use of this drug.

Cerebrospinal fluid has been collected for 10 frogs by cisternal puncture and analyzed by the method described. The mean reducing substance content was 13 mg. per 100 cc. less than that of plasma simultaneously collected.

Effect of Pituitary Removal on the Survival of Decerebrate Cats.—H. C. BAZETT (from the Laboratory of Physiology, University of Pennsylvania). Recent work has tended to discredit the idea that the pituitary is essential to life.¹ In view, however, of the presence of accessory pharyngeal glands of anterior lobe type, of a pars tuberalis extending over the infundibulum,² and of the identification of secretory cells of anterior lobe character extending into the tuber cinereum,³ it is certain that no complete removal on a physiologic basis has been attained without a complicating nerve injury. Symptoms are ascribed by some to the pituitary, by others to nerve lesions (particularly diabetes insipidus and adiposity) and Bourquin⁴ even attributes diabetes insipidus to irritation of a chemical mechanism existing in the corpora mamillaria. The decerebrate cat is of value in that the hypothalamic region may be left *in situ* while isolated from the rest of the brain, so that it could produce effects via chemical but not via nervous channels.

The technique of obtaining chronic decerebrate cats described in 1922⁵ has been improved, first, by using "Nembutal" as an anesthetic to diminish hemorrhage during and after operation; second, by keeping the animals in a warm moist room (21° to 22° wet bulb, 24° to 26° dry bulb) to decrease risks of infection and dessication. Rectal temperature is controlled by electrical resistance thermometers connected to a Leeds and Northrup recording potentiometer. By a system of selective switches and relays the temperature of each of a series of 4 animals is sampled for 1½ minutes every 9 minutes, and a heating light below the animal is automatically switched on or off as required.

The average survival time of 8 control animals, in which the pituitary and neighboring isolated brain was intact, has been greater than 11.8 days (min. 3.6, max. 28.5) even though several animals have been

deliberately killed for other purposes after 1 week. When the pituitary and the hypothalamic brain area have been removed, the average survival time (8 animals) has been 4.33 days (min. 1.25, max. 6.25). Death has occurred preceded by an initial but subsiding polyuria, loss of weight gradually decreasing in rate, a terminal rapid respiration without respiratory infection (also noted earlier⁶), and a tendency to vomit, but there has been little or no tendency to the convulsive movements observed in earlier experiments.⁵

Two animals died with this typical symptomatology without the pituitary being removed; in one (life 4.25 days) the brain stump was negligible but the pituitary intact, in the other (life 5 days) the pituitary was demonstrated histologically normal but the neighboring brain tissue was soft and degenerated.

The following provisional conclusions may be drawn:

1. Under the régime described with a food intake of 200 cc. of milk a day some chemical effect of the pituitary and surrounding brain tissue is essential for survival.

2. The chemical functions of this area are more readily attained when the anatomical relationship of the pituitary to the brain stem is not disturbed.

3. The hypothalamus itself is probably not essential, for survival has been observed in one case in its absence.⁵

My thanks are due to Mrs. Friedman, who assisted in developing the technique, to Dr. Friedman for making histologic sections of the pituitary, and to Mr. A. Afford and H. Goslyn for their careful nursing of the animals; also to the Abbott Laboratories for supplying "Nembutal."

1. Smith, P. E.: *Anat. Rec.*, 1930, **45**, 205.

2. Geiling: *Physiol. Rev.*, 1926, **6**, 64.

3. Berger, L.: *Presse. méd.*, 1930, **38**, 1729.

4. Borquin: *Am. J. Physiol.*, 1929, **88**, 519.

5. Bazett and Penfield: *Brain*, 1922, **45**, 185.

6. Bazett, Tychowski and Crowell: *Proc. Soc. Exper. Biol. and Med.*, 1924, **22**, 39.

The Effect of Toxic Doses of Irradiated Ergosterol Upon the Composition of Rat Bones.—J. H. JONES and G. M. ROBSON (from the Laboratory of Physiologic Chemistry and Laboratory of Pathology, University of Pennsylvania). The premise that irradiated ergosterol, at least in large amounts, can increase the absorption of calcium (and possibly phosphorus) from the intestinal tract and also mobilize this element from body tissue is being gradually substantiated. The most obvious source of body calcium is the skeleton, and several attempts have been made to show that inorganic constituents have been withdrawn from the bones during irradiated ergosterol intoxication. The results of chemical analyses of bone have been somewhat contradictory and misleading due primarily to the use of growing animals. Since there was a normal increase in the percentage of bone ash of the controls during the experimental period no reliable basis for comparison was available. In other cases insufficient vitamin D preparation was given to produce a toxic condition or so much was administered that the animals died before irradiated ergosterol had opportunity to exert any influence on the bones.

In the following experiments 36 rats divided into 3 groups were used. When placed on experiment the animals varied in age from 68 to 138 days. Two groups were used as controls, the first of which was killed at the beginning and the other at the end of the experimental period. Sufficient irradiated ergosterol was given to the experimental animals to cause toxic symptoms followed by death within 6 weeks to 2 months after the beginning of the feeding. The right femur from each animal was removed and analyzed for ash. The distal end of the other femur and the proximal end of the corresponding tibia were removed and fixed for histologic examination. Before ashing, the right femora were Roentgen-rayed in a group on one plate. The ash analyses revealed that, in general, there was a marked decrease in the percentage of bone ash; the maximum reduction being about 10 per cent when compared with a litter-mate control. Upon histologic examination it was found that the cortex of the shaft had become very porous. The porosity was due to a complete destruction and resorption of organic as well as inorganic matrix, and the spaces so formed were filled with marrow. Under the high power magnification many osteoclasts were discernible which would indicate an osteoclastic destruction of the bone. There was no evidence of a simple chemical removal of the inorganic salts. The densities of the roentgenograms were determined with a densitometer.* It was found that the densities of the negatives of the bones of the experimental animals were about 10 per cent greater than those of either of the control groups. Since the measurements were made on the negative, the densities of the bones themselves would be correspondingly decreased. There were a few discrepancies between the chemical, histologic and Roentgen ray findings but these occurred among the younger animals. All experimental animals above 100 days of age showed a loss of bone matrix as shown by chemical, histologic and Roentgen ray studies. No evidence was obtained to indicate that this action is specific for irradiated ergosterol. It is possible that chronic intoxication caused by other substances may produce similar effects.

* We wish to thank Professor Charles Weyl and Mr. Reid Warren of the Moore School of Electrical Engineering for making the densitometer determinations.

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ORIGINAL ARTICLES.

MEDICAL APPLICATIONS OF ANTI-COLIBACILLARY SERUM.*

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(From the Laboratory of Infectious and Epidemic Diseases.)

Numerous works published during the last few years have directed attention to the great frequency and importance of infections due to *B. coli*. It has been found that a certain number of ill-defined infectious states are due to this microörganism. Primary infection of the kidney and bladder caused by *B. coli* is extremely common and, when slight, is apt to escape recognition.

B. coli may be the active cause of grave septicemias, particularly in children. This organ may implant itself in any of the organs or tissues: brain (H. Vincent), meninges, endocardium, pharynx, intestine (infantile cholera, severe enterocolitis), liver (intense jaundice, H. Vincent), spleen, peritoneum (gangrenous appendicitis), Fallopian tubes, ovaries, uterus, respiratory apparatus (infantile broncho-pneumonia), and the bones and periosteum (H. Vincent). It is well known as a frequent cause of infection of the urinary apparatus, the prostate and the seminal vesicles.

In nursing infants the localization of *B. coli* in the kidneys gives rise to extremely grave suppurative pyelonephritis, which may escape recognition simply because it has not occurred to any one to collect the urine separately. In the adult, constipation and pregnancy are frequent underlying causes of suppurative coli-bacillary pyelonephritis both acute and chronic.

B. coli is not only dangerous by reason of its infective properties and its rapid proliferation in the blood, viscera and tissues, but also

* Translated by Edgar Erskine Hume.

on account of the toxin it produces. In previous studies, I have shown that there is not merely one colibacillary toxin. The bacillus secretes (1) a neurotropic thermolabile exotoxin, destroyed by a temperature of 72°C ., which causes widespread damage, sometimes indeed the destruction by true necrosis of the motor and sensory cells of the spinal cord. It also attacks the encephalon and the peripheral nerves and the sympathetic and vagus systems.

(2) Secondly there is an enterotropic thermolabile endotoxin, destroyed by a temperature of 96 to 98°C ., the ill effects of which are exerted on the intestine, the mucous membrane and the intestinal glands and Peyer's patches as well as upon the hepato-biliary apparatus. There results profuse diarrhea, desquamation and congestion of the intestine, damage to the liver and catarrh of the bile ducts, etc. Colon bacilli moreover contain a toxic protein which after resisting a temperature of 100°C . is able to kill mice.

From the strictly pathologic point of view, though contrary to general opinion, there is only one species of colon bacillus. On the strength of certain morphologic, chemical and cultural characteristics (mobility, indol reaction, hemolytic properties, sugar fermentation, action on neutral red, reciprocal inter-agglutination, etc.), it had been inferred that there was an infinite number of varieties of the colon bacillus. But, as I have shown, all these varieties have one property in common, namely, that of secreting a variable quantity of exotoxin and endotoxin, the former neurotropic, the latter enterotropic and hepatotropic. The "index of toxicity" is, in accordance with a general law in microbiology, very variable according to the particular organism.

Close clinical observation of patients reveals symptoms more particularly due to one or other of the toxins or to their association. In the latter case, apart from the gastro-intestinal disturbances (diarrhea, jaundice, etc.) we may meet with more or less severe nervous manifestations such as stupor, delirium, restlessness, late paralyses, psychasthenia, mental depression, melancholia, etc. One or other of these symptoms predominates according to the case.

Experimentally we can set up choleric symptoms in rabbits with persistent diarrhea and a low fever (endotoxin) or even nervous symptoms such as ascending paralysis, monoplegia, fantastic behavior. A rabbit injected with toxin would bite the ears of the other rabbits, both male and female, as well as guinea-pigs which had been placed in the same cage. These last-named symptoms were the effects of the neurotropic exotoxin.

As a result of my bacteriologic investigation of the colon bacillus and its toxins as well as other experimental data, I was led to prepare a therapeutic anti-colibacillary serum, at once anti-infective and anti-colibacillary. This serum, employed in numerous cases of grave colibacillosis, yielded very rapid and conclusive results.

In 1925 I published the first instances of cure by the use of this

anti-colibacillary serum. It was a case of long standing severe infection (suppurative pyelonephritis) which had proved refractory to every kind of treatment. Since that date various publications have confirmed the efficacy of this method of treatment in acute and chronic infections due to *B. coli*.

Medical Affections in Which Its Use is Indicated. *Colibacillary septicemia* is of rather frequent occurrence. Its symptoms closely resemble those of typhoid and paratyphoid fevers, A, B, or C, but there is no eruption of lenticular spots (H. Vincent). The diagnosis is established by blood culture. In infants it is a very fatal disease. In the adult the death rate is about 4 per cent and the disease is apt to be very protracted.

Anti-colibacillary serum treatment promptly brings about recovery from this septicemia. Under the influence of the injections of serum (20 to 40 cc. per day), the temperature almost invariably returns to normal after the second or, at latest the third, day. The stupor subsides, the tongue becomes clean, the spleen returns to its normal size, the albuminuria disappears, and the patient soon begins to ask for food.

This affection sometimes follows severe physical overstrain. I have notes of two instances of this.

Case Abstracts. CASE 1.—A young man, aged 21 years, following over-exertion in sports in the middle of summer, developed very severe protracted septicemia. Blood culture revealed the *B. coli*. On the 38th day of his attack the temperature was still just over 103° F. He had albuminuria with signs of myocarditis, considerable loss of weight and pronounced weakness. Then four subcutaneous injections of 20 cc. of anti-colibacillary serum, at the rate of one each day, cut short the disease. The temperature fell 36 hours after the first injection, the pulse became normal and the patient recovered without any complication or recurrence.

CASE 2.—Another instance of colibacillary septicemia of extraordinary gravity was in a girl, aged 3 years. There was hyperpyrexia of the continuous type, acute cholangitis with jaundice, intense acute nephritis with general anasarca involving the limbs, trunk, and face, complete torpor, nystagmus, clonic contractions of the face, lips and lower limbs, etc.

The prognosis pointed to imminent death. This child was given five injections (one a day) of anti-colibacillary serum with rapid, complete disappearance of all these formidable symptoms. On the third day the temperature fell to normal and the child asked frequently for food. The jaundice and edema disappeared in less than a week. The nervous symptoms cleared up after the second day. The little patient made a rapid, complete recovery.

CASE 3.—Another not less striking case was that of a woman, aged 28 years, 6 months pregnant, who was suffering from acute colibacillary septicemia with suppurative pyelonephritis, almost complete anuria, torpor, an earthy color of the skin, temperature of 105° F., jaundice, infective purpura, etc. This patient, in the wards of Professor Chevassu, appeared to be condemned to die in the course of a few days. The desirability of inducing abortion was discussed but my colleague objected, asserting that the only effect would be to kill both mother and child. The kidney pelves were drained for 24 hours and 40 cc. of the serum was injected daily for several days. The

temperature returned to normal within 36 hours. On the fourth day the patient got up and ate a mutton cutlet belonging to another patient, unknown to the doctor and nurse. She made an excellent recovery and 3 months later was delivered of a fine child, without any complication, infective or otherwise.

These instances show that we are effectually armed against the most alarming forms of the blood infection set up by *B. coli*.

Suppurative Pyelonephritis. This must be mentioned among the commonest localizations of colibacillosis accompanied or not by cystitis of the same kind. Of frequent occurrence in children just as in adults, often very refractory, this affection is also met with in the pregnant woman in consequence of the pressure exerted by the fetus on the right kidney and the intestine. Pressure on the renal vein further aggravates the stagnation of blood in the kidney. Whatever the cause may be, suppurative pyelonephritis yields to the anti-colibacillary serum treatment. It is as much a surgical as a medical disease. I shall deal with this in a later paper devoted to the surgical applications of anti-bacillary serotherapy.

The Gall Bladder and the Liver. Both these as I showed in 1893, are sometimes invaded by the coli bacillus in cases of grave jaundice.

CASE 4.—An elderly patient whose case was communicated to me by Dr. Verain, Chef de Laboratoire at the Nancy School of Medicine, was suffering from *B. coli* suppurative pyelonephritis of long standing (5 years), with cystitis and advanced anemia (1,600,000 red corpuscles). Shortly after she had a violent attack of cholecystitis accompanied by high temperature, diarrhea and grave septic symptoms. Urotropin in large intravenous doses, auto-vaccines and other forms of treatment had proved useless.

On and after October 3, 1928, this patient was given five injections (one a day) of anti-colibacillary serum. At that time her temperature was between 104 to 105° F. Within 3 days the temperature had fallen to normal. The urine became quite clear and the symptoms of acute cholecystitis had completely disappeared.

In these cases of cholecystitis we must, of course, begin by making sure that *B. coli* is really the cause of the condition by obtaining a specimen of bile by duodenal drainage. This bile is examined microscopically and bacteriologically and, after dilution, is inoculated in different suitable culture media for the identification and differentiation of the bacillus.

Disorders of the Nervous System. *B. coli* may produce nervous complications by its neurotropic toxin (exotoxin). This as a matter of fact may attack the central nervous system, the peripheral nerves or the sympathetic or vagus nerves, often setting up immediate symptoms, though these may only supervene later on. It does not always occur to us to refer such symptoms to their real causes.

Experimentally, progressive ascending paralysis consequent upon acute or chronic myelitis can be readily induced in the rabbit by the injection of colibacillary toxin. It is quite possible that some

of the cases described as Landry's ascending paralysis in man are due to intoxication produced by the neurotropic exotoxin of *B. coli*. Moreover, also in man, paraplegia may supervene in renal subjects (Gilbert and Lion) and in patients who have formerly suffered from colibacillary septicemia. I have seen the appearance of slow paraplegia, coming on 5 years after recovery from general infection of this kind, complicated by pyelonephritis and suppurative cystitis. The bacillus, isolated in the course of the septicemia, secreted a very active neurotoxin which rapidly paralyzed rabbits.

The clinical interest of such data is very great because they enable us to understand certain nervous affections of indeterminate origin. No doubt coli-bacilluria may and often does supervene secondarily in paraplegics, but it must be recognized that colibacillosis may itself directly determine these lesions of the spinal cord. In such case we find in experimental animals and in man, pronounced diffuse changes in the motor and sensory cells of the cord (H. Vincent, 1922).

As soon as these symptoms make their appearance, the anti-colibacillary serum should be injected forthwith because it, by virtue of its powerfully antitoxic properties (antimicrobial as well), will neutralize the toxins and bring about recovery. The administration of the serum should be continued until all the symptoms have disappeared.

Certain species of *B. coli* secrete extremely active neurotropic toxins.

CASE 5.—An instance of this occurred in a woman, aged 70 years, who was suffering from very long standing, grave double suppurative pyelonephritis. Her urine contained a predominance of *B. coli*; but also staphylococci, enterococci, diphtheroid bacilli, and anaërobes.

This patient had reached an extreme degree of marasmus. She was unconscious, delirious, comatose, quadriparetic, was unable to speak or to recognize her husband and children, was suffering from fecal and urinary incontinence. Death at an early date appeared inevitable. The condition had been diagnosed uremia. In reality she had colibacillary toxi-infection.

She was given 40 cc. anti-colibacillary serum a day for 8 days, as well as my new antistreptococcal serum, in view of the presence of streptococci in the urine. This patient recovered consciousness in 3 or 4 days. The paresis of the arms and legs, the fecal and urinary incontinence, the aphasia and the mental clouding entirely disappeared. She resumed her usual life. She was able to converse, eat, telephone and look after her household, and survived for about 2 years. Colibacillary toxi-infection was therefore indubitably the cause of these grave nervous disturbances.

Cases of this kind have greatly astonished practitioners who have witnessed them. I myself, endowed with scientific skepticism, only accepted them as authentic after having directly controlled the data.

I may recall on the other hand the formidable nervous symptoms (absolute torpor, delirium, clonic and tonic convulsions of the face and limbs, nystagmus, etc.) in the child described above and who

completely recovered with extraordinary rapidity from the septicemia and from all the accompanying symptoms.

Gastro-intestinal Disorders. The study of the nervous or neuropathic symptoms present in certain cases of *B. coli* septicemia, as well as in certain cases of acute or long standing pyelonephritis and, lastly, in a large number of cases of refractory enteropathies (enterocolitis, chronic muco-membranous enteritis) which are neither tuberculous nor parasitic, has led me to investigate the relationship of these complications to colibacillary intoxication itself. In patients infected by *B. coli*, we often get more or less serious gastro-intestinal disturbances and at the same time characteristic neuropathic reactions: on the one hand, visceroptosis, ptosis of the colon, intestinal spasm, painful colic, attacks of diarrhea following periods of constipation, mucous or bilious stools, etc.; on the other hand, excessive mental irritability alternating with periods of depression, incapacity for work, melancholia, outbursts of weeping, refractory insomnia, headache, symptoms of neurasthenia or even by psychasthenia merging, it may be into suicidal tendencies.

I have brought before the Academy of Medicine of Paris* (April 19, 1930) instances of these morbid states in which the double intoxication of the patient by *B. coli* enterotoxin and neurotoxins were completely verified, as all the symptoms of enteritis and neuropathy disappeared in a few days after the influence of anti-colibacillary serum. And these symptoms have not recurred.

Among such cases was a woman who had been ill for 5 years.

CASE 6.—Another was that of a man, aged 72 years, who had been suffering from refractory chronic enterocolitis since 18 years of age. He had therefore been ill for 54 years. He had traveled all over Europe in search of health and had consulted numerous physicians without any other result than the confirmation of the diagnosis of a "muco-membranous enterocolitis." The various methods of treatment, and especially vaccines including autovaccine, had conspicuously failed. His neuropathic state was very bad.

Having received six injections of the anti-colibacillary serum this patient was cured in a few days. From this time forth he had regular bowel motions, no longer presented any nervous disturbances and could partake of ordinary food. The serum had given this 78-year-old man, by a striking improvement, the sense of having been restored to normal health, a feeling which he had not had since he was 18 years of age. Seven months later he stated that "his health had remained quite remarkable such as it had never been since his youth" (H. Vincent, *Académie de Médecine*, Paris, April, 29, 1930).

Nor is this characteristic case an isolated one. I have witnessed recovery in cases of much shorter standing than the preceding one but suffering nevertheless from intestinal disturbances with diarrhea and grave neuropathic symptoms, obliging them persistently to follow, without appreciable result, a very strict regimen and some-

* Vincent: Rôle de la toxi-infection colibacillaire dans certaines entéropathies chroniques. Action de la sérothérapie anticolibacillaire dans ces états morbides, *Bull. Acad. de méd.*, Paris, 1930, 103, 431.

times incapacitating them for work. We all know how difficult it is to bring about a cure, or even improvement, in these enteropathic neuropathic subjects.

The very rapid disappearance of this complex group of enteritic and neuropathic symptoms as soon as we had administered the specific anti-colibacillary serum, demonstrates that *the etiology and pathogeny of chronic entero-colitis, sometimes referred to as mucous or muco-membranous colitis*, must be regarded from a new angle.

It should be considered as a toxi-infectious disease, though perhaps more toxic than infectious. It is consequent upon the absorption in the small, as well as in the large, intestines of thermostable enterotoxin (endotoxin) and of thermolabile neurotoxin (exotoxin) secreted in contact with the intestinal mucosa by innumerable colon bacilli which normally vegetate in the digestive tract. This micro-organism, as is well known, predominates in the intestines. We can count a hundred billion a day in the stools of the healthy subject. The enormous proliferation of this parasitic organism is inoffensive in the healthy subject, because the liver, the bile and the pancreatic and intestinal secretions are normal, and the neutralizations of the toxins is therefore continuous and complete. I have, on various occasions, repeated my researches into this physio-pathologic problem and I will sum up in a few words my views on the subject.

In the normal state the bile is the principal agent of disintoxication of the intestine. The bacteria which vegetate there in prodigious numbers and elaborate their dangerous poisons are however rendered innocuous because the bile readily and completely neutralizes their toxins as they are secreted. (H. Vincent.) The essential element of the neutralizations of the microbial poisons poured into the intestine is the normal soaps contained in the bile: the oleate, stearate and palmitate of sodium (H. Vincent, 1907). Hitherto sufficient importance has not been attached to the physiologic and biologic rôle played by these bile soaps. Yet their proportion and their fixity show that there can be no question of an indifferent principle. Analyses made by Hoppe-Seyler show that normal bile contains 1.39 per cent by weight of soaps, principally in the form of palmitate of sodium. According to Hammarsten, human bile contains 1.01 grams of fatty acid soaps per 1000. Now, as I have shown in various publications in 1907, and 1908, and 1909, since confirmed by numerous researches in other countries, especially in the United States (Larson and Nelson), these soaps have even in almost infinitesimal proportions, the property of destroying the most dangerous toxins (tetanus, diphtheria, colon bacillus, *B. edematiens*, septic vibrio, etc.). For instance from two to four millionths of a milligram of palmitate of sodium neutralizes an otherwise lethal dose of tetanic toxin.*

* The soaps apparently do not really destroy the toxins but are thought to envelop the particles of toxin in a film, thus transforming them into what I have termed "*cryptotoxins*." The bile salts are, strictly speaking, very slightly antitoxic.

I am inclined to think that patients suffering from chronic muco-membranous entero-colitis originally suffered from hepatic insufficiency and consequently an insufficiency, especially qualitative, of the bile secretion, the soaps not being present in their normal proportion in the bile.

In patients who are in a state of hepato-bacillary insufficiency the normal multiplication of the intestinal bacteria, more particularly of the colon bacillus, becomes a danger, the greater since these subjects are usually constipated. Furthermore as the soluble poisons secreted by these microorganisms are no longer completely neutralized by their continuous absorption, they become a continuous danger. This explains the whole of the symptoms observed in enteritic patients. The following very variable symptoms characterize such intoxications: pallor, subicteric hue or actual jaundice, tenderness of the liver or gall bladder (representing the fixation of the endotoxin on the hepato-biliary apparatus). On the other hand the spasm of the colon, colic, constipation or fetid diarrheic outbursts resulting from this spasmodic state, the contractures, either in the right or the left half of the large intestine, are the effects of the local intoxication of the vagus and the sympathetic, by the two toxins I have described. The neuropathic or constitutional troubles (asthenia, myalgia, irritability, depression sometimes giving rise to ideas of suicide, the sensation of anguish, the refractory insomnia, etc.), characterize the intoxication of the central nervous system more particularly by the neurotoxin (exotoxin) of *B. coli*.

I have endeavored to verify the colibacillary origin of these toxi-infectious phenomena by studies of blood reactions (the precipitative or agglutinative power of the patient's blood, fixation of the complement), but the results have been irregular and uncertain. More to the point is the finding of abundant *B. coli* in the urine, though this is not always the case. But in a high proportion of cases, there is one important confirmation of the elective and preponderant action exerted by the colon bacillus in producing the preceding group of symptoms and that is the rapid and often immediate disappearance of all these intestinal and neuropathic disturbances under the influence of treatment with the anti-colibacillary serum.

This new conception, at once of great theoretical and practical interest, leads to a rational understanding of the pathogenesis of an affection the nature of which is much in debate. Lastly, and most important, it culminates in the cure, hitherto very slow and very difficult, of this disease, since mucoid or muco-membranous entero-colitis may last for years, sometimes throughout life, and greatly handicap the patient's existence.

In a recent publication I called attention to the toxi-infectious, or more precisely, colibacillary origin of certain states of dementia. I have had under my care a case of a young man, aged 18 years, with dementia precox, following colibacillary septicemia. Then too

I have recorded notes of a patient, aged 47, who for 6 months had been suffering from extraordinarily obstinate constipation and ultimately from urinary colibacillosis. This patient presented symptoms of hypochondria with fugues, delirious mania, ideas of persecution and suicide, and intense mental depression and mutism. At the same time he suffered from well-marked digestive disturbances and total loss of appetite. He was cured after six injections of 40 cc. each of anti-colibacillary serum.

These examples deserve to be placed on record because they may in some cases provide an explanation, hitherto very uncertain, of various mental disturbances, and may conceivably result in their cure. In such cases, therefore, it is advisable to inoculate an animal with the urine in order to ascertain whether the *B. coli* be present, and systematically to investigate whether in the patients' antecedents, there have not been grave, persistent gastro-intestinal disturbances, chronic constipation, or appendicitis (a very frequent cause, as I have shown, of pyelonephritis and coli-bacillaria) or even of a septicemic infection, clinically resembling typhoid or paratyphoid fever, which may have been unrecognized colibacillemia.

It is important to commence the anti-colibacillary serum treatment in these cases as early as possible. As with diphtheritic paralyses where the fixation of the toxin in the nerve centers may become irremediable, so *pari passu* the colibacillary toxin, if the serum treatment be delayed, may cause lesions of the nerve centers which will prove refractory to this otherwise energetic treatment.

INFECTIVE ASTHMA: INDICATION OF ITS ALLERGIC NATURE.

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THERE is no doubt but that bacterial infection of the respiratory tract may cause asthma of an acute and paroxysmal as well as of a chronic form. There is, however, a great deal of doubt whether or not asthma of infective origin should be considered as an allergic reaction. Some recent studies of this condition from two different angles may help in the solution of the problem. They deal, first, with heredity and, second, with the eosinophil response.

Heredity has been shown to be important not as a cause but as a factor that may create in the offspring of sensitized antecedents the capacity for or tendency toward that form of allergy typically

exemplified by the seasonal hay fever from pollen. The report of Vander Veer and myself,¹ in 1915, has been abundantly confirmed and accepted. In a later study by the author and Spain² we excluded cases not giving the immediate positive skin test. We were, therefore, dealing with that form of allergy in man characterized by a sensitization of the skin and, as a rule, by the presence of circulating antibody in the blood.

In this skin-sensitive group hereditary influences are evident, but studies on the hereditary factor in the so-called nonsensitive group of asthmatics have not appeared in the literature. With some exceptions, the terms "nonsensitive" and "infective" are practically synonymous, as applied to asthma. No immediate urticarial reaction on skin test with bacteria or their products has been found to have etiologic or diagnostic significance and, as would be expected, skin-sensitizing antibodies are not demonstrable in the blood in such cases.

We have now collected data on a series of cases of asthma that are semi-selected. By that I mean that the group comprises consecutive cases, selected only to the extent that they were studied to a satisfactory diagnosis and were cases in which an adequate family history was obtained. There resulted 688 cases. Grouped according to cause as nonsensitive (infective), sensitive (atopic) and combined, the cases are arranged, depending on the age of onset of asthma, in different age groups for comparison. The figures are tabulated in Table 1. Divided in this way some age groups are

TABLE 1.—CLASSIFICATION SHOWING HEREDITARY INFLUENCE IN THE SKIN-SENSITIVE AND THE INFECTIVE TYPE OF ASTHMA.

Asthma onset, age.	Total number cases.	Classification.						Positive antecedent history.					
		Atopic.		Infective.		Combined.		Atopic.		Infective.		Combined.	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0 to 3 . .	106	54	50	33	31	19	19	36	67	30	91	14	74
3 to 5 . .	42	25	59	7	17	10	24	16	64	6	86	8	80
5 to 10 . .	70	48	68	13	19	9	13	34	71	9	69	5	56
10 to 15 . .	55	36	65	13	24	6	11	24	67	6	46	6	100
15 to 20 . .	79	50	63	17	22	12	15	24	48	8	47	6	50
20 to 30 . .	123	70	57	39	32	14	11	31	44	14	36	6	43
30 to 40 . .	117	44	37	50	43	23	20	13	30	17	34	7	30
40 to 50 . .	54	15	28	32	59	7	13	5	33	8	25	4	57
Over 50 . .	42	7	17	31	74	4	9	0	0	8	26	1	25
Total . .	688	349	51%	235	34%	104	15%	183	52%	106	45%	57	55%

necessarily small. The high percentage (82 per cent) of positive antecedent histories of allergy in the purely infective group up to the age of 10 years, as contrasted with 67 per cent for the same age group in the skin-sensitive (atopic) cases and a positive antecedent history of allergy in 45 per cent of the entire infective group of

106 as contrasted with 52 per cent of 183 atopic cases indicates I believe, that the underlying biologic capacity for sensitization transmitted to the offspring by allergic antecedents is similar in the infective and the atopic cases.

We are not here so much interested in the fact that in 195 cases of asthma the antecedent history was one of asthma in 66 per cent and of other atopies in 34 per cent. This is somewhat lower than the 80 per cent obtained by Clarke, Donnally and Coca.³ It seems important, however, that in a specially studied small group of 66 infective asthmas the antecedent history was one of pollen hay fever in 29 per cent. How many of the remaining 71 per cent had antecedents whose reaction was to noninfective causes could not be accurately determined, but there were a number. *Vice versa* not infrequently we find in atopic asthma an antecedent asthma of infective origin. We have not been able to study directly antecedent and descendant asthmatics in sufficient number for statistical figures, but the facts stated indicate not merely a similarity but rather an identity of the transmitted biologic factor in nonsensitive and sensitive asthmatics.

The second angle from which we may derive some light on the possible allergic nature of infective asthma is obtained by a study of the eosinophil cells in asthmatics of the sensitive and nonsensitive types. The difficulties of such a study are enhanced by the lack of knowledge and agreement among hematologists on such points as the origin and function of this cell in normal and pathologic states and the source and nature of the acidophilic granules. I shall only summarize from the very extensive literature on the subject the points dealing with questions of immediate interest. Of the monographs on eosinophilia those of Downey⁴ and Ringoen⁵ are most useful on account of the careful and critical survey of preceding literature as well as their own contributions.

Normally the eosinophils of the blood may be formed in the bone marrow by a homoplastic, *i. e.*, a mitotic, form of development, but more largely they are believed to develop by a heteroplastic differentiation from nongranular mononuclear marrow cells and, in some mammals, in the hemolymph nodes. Ringoen⁵ states (p. 36): "Many eosinophil leukocytes are developed in the hemolymph nodes, for numerous mononuclear forms are present."

As to the nature and origin of the acidophilic granules of the cells there is great diversity of opinion. That the granules are exogenous material taken up by phagocytosis is maintained by Weidenreich and Schott, Sabin, Gutig, Bodertscher, Lewis and others,* while Maximow,* Downey⁴ and Ringoen⁵ seem clearly to have shown that at least as far as normal bone marrow is concerned the granules are an endogenous differentiation of the cytoplasm of nongranular cells and in their earlier stages may be basophilic.

* Quoted from Downey: *Loc. cit.*, pp. 153 and 194.

An extramedullary or histogenous origin of eosinophil cells has been observed under certain experimental conditions, which we now recognize as those that produce a hypersensitive state. This view is supported by Weidenreich, Maximow, Downey, Gutig, Pappenheim and Dominici. Such a development was first observed by Weidenreich following repeated intraperitoneal injections of red blood cells, and he supposed the eosinophil granules in cells of the taches laiteuses of the rabbit omentum were hemoglobin phagocytosed by lymphocytes. This erythrocytic origin of the granules had been disproved by Maximow, Sternberg, Downey and particularly by Ringoen in his monograph in 1922.

In 1912 Schlect and Schwenker⁶ studied eosinophils in anaphylaxis. These authors noted a marked blood eosinophilia in guinea pigs after shock and showed eosinophilic infiltration of lung and peribronchial tissues, peritoneal fluid and tissue fluid from areas of skin edema (Arthus phenomenon). They believed that the eosinophil cells were drawn to the tissues from the blood and marrow and were not formed at the site of reaction.

Ringoen's more recent work (1922) substantiates the findings of these authors. He agrees that the eosinophil cells in peritoneal fluid produced by repeated intraperitoneal injections are not locally produced, chiefly because of the associated blood eosinophilia. He did find an histogenous tissue eosinophilia after a single subcutaneous injection of hemoglobin. Tissue from an injected site was examined from the third to the twelfth day and mononuclear eosinophil cells, which he believes to be clasmatocytes, were found. He states further (p. 55): "A résumé of the literature . . . shows that a number of authors have derived eosinophilic leukocytes from various sources. Lymphocytes, large mononuclear, plasma cells and adventitial cells have all been taken into account as the parent cell of tissue eosinophils." Thayer,⁷ in 1897, and Brown,⁸ in 1898, showed the presence of eosinophils in muscle tissue infected with trichinae. They believe the neutrophils were transformed in the reaction, but most hematologists do not agree with this conclusion.

Hickling gives a per cent as the normal for eosinophils in blood of man. An eosinophil increase is seen in man in metazoan infestations, eczema, asthma, anaphylactic shock and serum disease and, as Hickling¹⁰ has shown, it may be a postinfective phenomenon. It also occurs in scarlet fever and during the third week of liver feeding in pernicious anemia.¹¹

In asthma the presence of a blood eosinophilia has long been known, but it is so inconstant and irregular that no significance can be attached to it. It is certainly more apt to be present when blood is examined during the attack. In an article by the writer,¹² in 1918, 90 cases were reported. The eosinophil count was above 4 per cent in 68 per cent of the cases with positive skin tests and in 47 per cent of those with negative test.

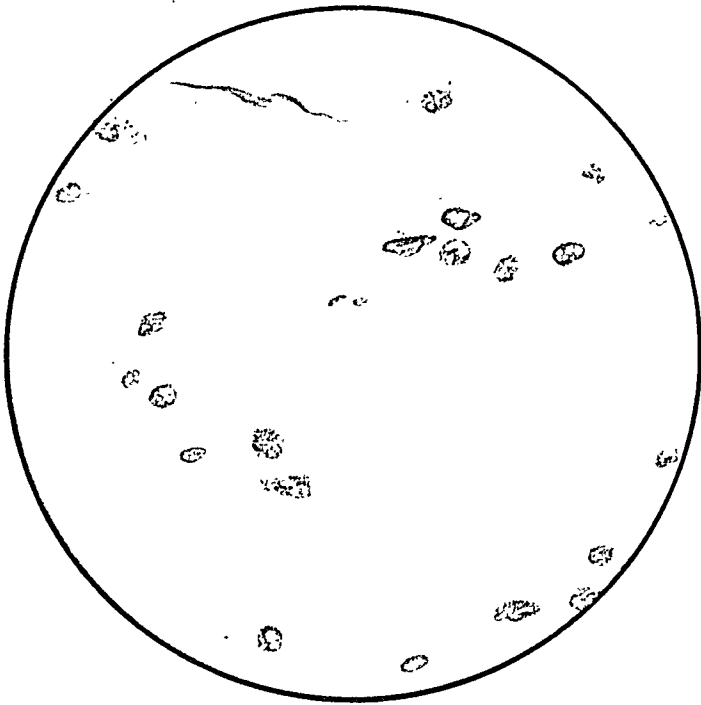


FIG. 1—Nasal washings.

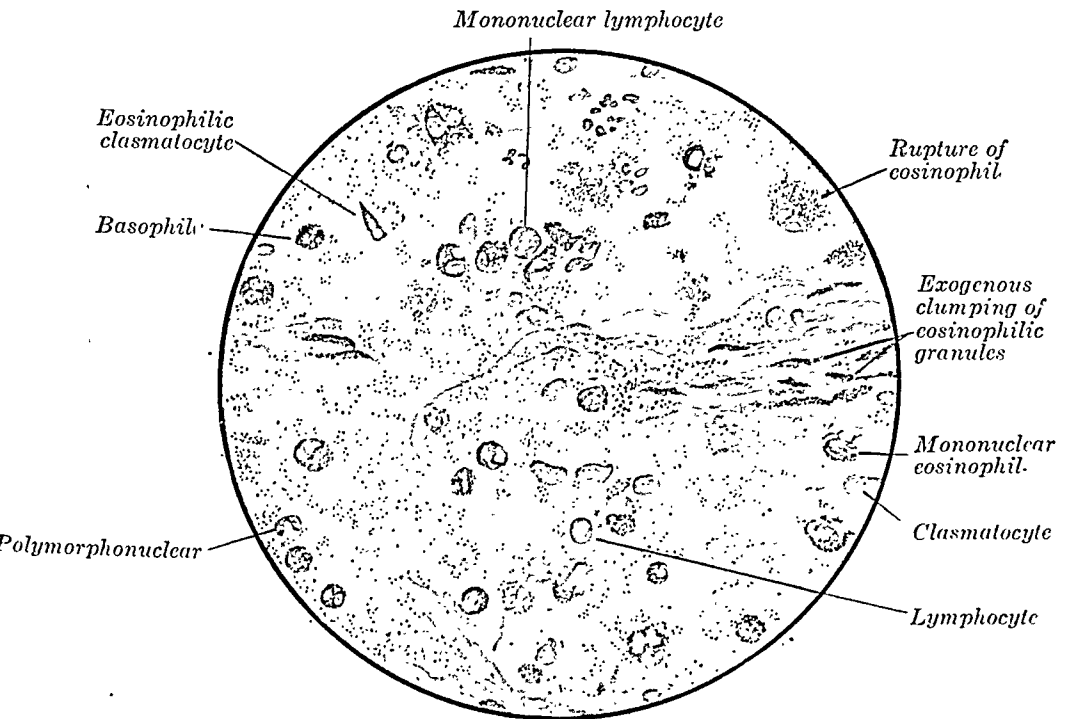


FIG. 2.—Sputum. Blood showed 4% eosinophils.

Marked eosinophilic infiltration of the bronchi has been described in most of the pathologic reports on asthma since Huber and Koessler's¹³ noteworthy contribution in 1922. In view of the fact that at autopsy many eosinophil cells are seen in the bronchial wall, it can scarcely be questioned that these cells in the sputum are derived from the tissues of the bronchi directly. During asthmatic attacks eosinophil cells may be found in the sputum in practically all cases with repeated examinations, according to our previous studies.

A similar type of eosinophilic infiltration is also well known in the so-called hyperplastic or hypertrophic forms of rhinitis and sinusitis with or without polypi. In a recent paper Coates and Ersner¹⁴ report on examinations of the antral membrane in 50 cases, as follows: "The cellular elements in the tissues were: Round-cell infiltration, lymphocytes, polymorphonuclear leukocytes and occasional eosinophils in the nonasthmatic group. The asthmatic membrane presented a predominance of eosinophils with some polymorphonuclear leukocytes and lymphocytes."

Kountz and Alexander¹⁵ examined the nasal mucous membrane in 1 of their cases dying of asthma and found many eosinophil cells. Hansel¹⁶ has recently reviewed over 1000 cases studied by him in which nasal and sinus pathology existed in allergic individuals, and he notes the almost constant presence of eosinophil cells in such tissue. Just as has been noted for sputum, eosinophil cells are abundant in the nasal and particularly the antral discharge. Eyerman¹⁷ reported these cells in 72 per cent of a hypersensitive group and in 9 per cent of the nonsensitive group.

In practically all of these reports one is led to infer, or else the statement is made, that this eosinophilia of tissues and secretions of bronchi and sinuses is an allergic reaction and, therefore, cannot be due to the bacterial infection alone. In fact Hansel says in his sixth conclusion: "The part played by bacteria as etiologic factors in nasal allergy has not been proved, and the general consensus of opinion is that bacteria are secondary invaders." Huber and Koessler,¹³ discussing the eosinophil infiltration of bronchi in asthma, say: "Its constant absence in certain forms of bacterial asthma is regarded as one important piece of evidence that there are types of asthma that may not be of allergic origin." To this point of view we take exception and will give reasons for believing that the eosinophil cell represents an allergic reaction of tissue to bacteria or their products.

Since our earlier report,¹² in 1918, we have been increasingly impressed by the presence of blood eosinophilia in asthma of purely infective origin, and during the past few months have collected data*

* I am greatly indebted to my associate, Dr. R. C. Grove, for his diagnosis on the nasal condition of these patients and to Miss Winifred Kelly, whose special training in hematology has provided unusual technical assistance.

which while not extensive will bear presentation now. The cases have been carefully studied, tested and classified as shown in Table 2. The groups as arranged are self-explanatory. In Groups

TABLE 2.—EOSINOPHIL STUDY ON 131 ACTIVE CASES.

Group.	Blood.		Sputum.		Sinus discharge.		No. with eosinophils low in blood, but abundant in sputum and sinus discharge.
	No. exam.	No. over 5%	No. exam.	No. with eos. abundant.	No. exam.	No. with eos. abundant.	
I. Asthma: infective only	31	19*	13	13	16	13	7
II. Asthma: infective (also other allergens)	13	8	3
III. Asthma: infective and atopic	32	24	1
IV. Asthma: atopic	18	8†	1	1	1
V. Coryza: infective allergy	15	7	10	6	3
VI. Urticaria	13	1
VII. Chronic sinus infection	9	0	9	1	9	0	...

* 9 above 8%; maximum, 27%.

† 1 above 8%; maximum, 9.5%.

I and II infection is the sole cause of asthma, but it was thought that infection in cases with other allergies of the skin-sensitive type (Group II), such as pollen hay fever, though not active at the time of examination, might yield higher results than the purely infective asthmas (Group I). This does not seem to be the case. We find that a blood eosinophilia is not only more frequent but it is also on the average higher in infective asthma than in the asthma caused by substances to which a positive cutaneous test was obtained (Group IV).

That the eosinophils of sputum and antral exudates are probably of local tissue origin and not myelogenous is indicated: (1) By the fact that 15 cases in Groups I to V, with normal differential counts of the peripheral blood, showed abundant eosinophil cells in the secretion or exudate of bronchial and nasal mucous membranes; (2) a careful study of such smears also indicates that the eosinophil cells of the exudates are not all morphologically similar to those of the blood taken at the same time.

The eosinophilic leukocytes of the blood are typical polymorphonuclear cells, while the eosin-staining cells of the exudates are not only polymorphonuclear but often more largely mononuclear, resembling both lymphoid cells and reticuloendothelial cells.

Reproductions of characteristic slides showing these findings were made from smears of antral and bronchial secretion in a boy, aged 13 years (No. 3466), with an acute upper respiratory infection and associated asthma. His blood showed 4 per cent eosinophils. This was his first attack of asthma since tonsils and adenoids were removed 5 years before.

In many cases the eosinophil granules are abundant throughout

the smears of the exudates and do not appear to have the grouping that is characteristic of ruptured eosinophil cells. This indicates that the acidophilic granules are formed outside the cells and are later ingested by all cells with phagocytic capacities, and under these conditions are strictly exogenous. This agrees with Downey's statement (p. 154) of Weidenreich's material which he examined: "All possible intermediate stages lead from the free granules to the fully differentiated eosinophil leukocyte."

In experimental anaphylactic shock eosinophil cells represent some phase of the allergic reaction, and since this reaction is a systemic one, medullary stimulation ensues with resulting blood eosinophilia.

We may hypothesize then that in asthma and in hay fever of the skin-sensitive type, blood eosinophilia results only when the allergic reaction is sufficiently general and systemic to affect the bone marrow. Sternberg¹⁸ has shown that during active hay fever eosinophilia generally, though not invariably, occurs, and Cohen, Ecker, Breitbart and Rudolph¹⁹ proved that pollen may be absorbed from the nasal mucosa into the circulatory blood and so effect a systemic bone-marrow response.

So in infection, whether it be scarlet fever, empyema or asthma, the eosinophil production which may result may be regarded as a sensitization phenomenon equally as well as it is so regarded in serum disease and experimental anaphylaxis. When the infection is localized, as in the sinuses, an allergic reaction to bacteria may result, with subsequent formation of eosinophil cells in the infected tissues and thence in their secretions, but this only occurs in those individuals capable of such sensitization. For example, in chronic suppurative sinus infection without asthma it is rarely found in the discharge or in the blood. Only one of our 9 cases showed an excess in the sputum, in none was there an increase in the blood, and antral pus showed none.

In infective asthma secondary to sinus disease an excess of eosinophil cells in the sputum and antral discharge is practically a constant finding, whereas an increase in the blood is found in but 61 per cent, and in our series, in Groups I and II, 10 cases with normal blood eosinophil content showed excess of eosinophil cells in the sputum and antral discharge. The opposite condition of increased blood eosinophilia with absence of eosinophil cells in sputum and antrum has not been observed by us in infective asthma secondary to sinus disease.

These facts lead us to believe that in this condition the eosinophil production is a local histogenous one and represents a local bacterial allergic reaction. If the particular stimulus is sufficiently absorbed to affect the bone marrow a blood eosinophilia would secondarily result. By such an hypothesis only can we explain the greater frequency of eosinophil cells in nasal and bronchial membrane and

secretion than in the blood. Support to this view is given by the fact that the histogenous eosinophil cells are not all morphologically like those of the blood, hence the theory that they are drawn to the tissues from the blood is not tenable, nor does such a surmise explain the presence of free acidophilic granules in the sputum and nasal discharge.

Very little has heretofore come of the study of eosinophilia, though its relation to asthma has long been known. The present study contributes at least one fact that I believe of basic importance, namely, that an eosinophilia, local or general, is as important a part of the cellular response in asthma of infective origin as in asthma of the skin-sensitive type. It is an immunologic, or, more specifically, an allergic response comparable to precipitin, agglutinin or other antibody.

Summary. 1. Asthma of infective origin appears to be subject to hereditary influence. This, of course, only proves that asthma, whether of the infective or skin-sensitive type, is the offspring of hereditary influences. But the facts that 15 per cent of all asthmas are combined sensitization and infective types, that skin-sensitive allergies are frequent in the antecedents of infective asthma and that the opposite condition also obtains, all lend support to the view that both types may be regarded as of the same nature.

2. Eosinophilia may be regarded as an allergic phenomenon. Experimentally it is produced only under conditions which are regarded as favoring sensitization. Local eosinophilia of histogenous origin is believed to be shown. Eosinophilia is as frequent in asthma of infective origin as in that of the skin-sensitive type.

3. Infective asthma may be regarded as an allergic reaction quite as properly as is the skin-sensitive type, although the immunologic reactions in the two forms are not identical.

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STUDIES IN PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION.*†

I. TWO NEW METHODS FOR DIRECT AND INDIRECT OBSERVATION.

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IN recent papers we have endeavored to stress the importance of bronchial obstruction in various types of lung pathology. Fundamental researches on the relation of bronchial obstruction to pulmonary disease were done as far back as 1844 and 1846 by Mendelssohn¹ and Traube,² who obstructed the bronchi of animals with shot, paper and gum arabic and produced atelectasis. It remained, however, for Lichtheim,³ in 1879, to show that ligation of a bronchus is followed by absorption of the gases of the air and atelectasis, but that a combined ligature of the bronchus to a lobe and its corresponding pulmonary artery is not followed by atelectasis. This was the first definite demonstration that the blood circulation through the lung is an indispensable factor concerned with the absorption of gases in the alveoli. Moreover, under direct vision he observed the actual speeds of absorption of carbon dioxide, oxygen and nitrogen by the lung. The objection could be raised, and not without

* This work was aided by a gift of Mrs. John L. Given in support of Surgical Research and a grant from the National Research Council Fund.

† A complete bibliography will accompany the third and last paper of this series, "A Theory of Atelectasis."

justification, that some of the observations of *Lichtheim* are non-physiologic in the sense that the thoracic cavity had been opened during the course of the experiments.

We shall not attempt to discuss here the train of thought by which bronchial obstruction has been correlated with atelectasis, post-operative pneumonia, lobar pneumonia and other pathologic states of the lung. In our previous papers^{4,5,6,7,8,9,10} we endeavored to give a comprehensive history and view of the subject in general and of the special importance of bronchial obstruction in the pathogenesis of pulmonary disease.

More particularly controversy has waxed keen concerning the etiology of postoperative atelectasis. We believe it may conservatively be stated that at the present writing the only definitely proven direct etiologic factor in its production is complete bronchial obstruction. We shall show in this series that in complete bronchial obstruction, by the normal play of gas exchanges a complete absorption of gases from the alveoli and atelectasis ensue. This concept will be elaborated in the second and third papers of this series, entitled, respectively, "The Behavior and Absorption Times of Oxygen, Carbon Dioxid, Nitrogen, Hydrogen, Helium, Ethylene, Nitrous Oxid, Ethyl Chlorid and Ether in the Lung" and "A Theory of Air Absorption in Atelectasis."

During the course of our studies we developed a technique for following closely under direct vision the gas exchanges within the lungs from the time of complete bronchial obstruction to the completion of atelectasis. The methods to be described have been unusually valuable in giving us an insight into the finer mechanism of the production of atelectasis and the exchange of various gases through the pulmonary endothelium. In addition, they offer an excellent opportunity for further studies on the lung, be it from the standpoint of the thoracic surgeon, the anesthetist, the internist or the physiologist.

We shall describe below the indirect, or "closed-chest" technique, and the direct, or "open-chest" technique. With both methods complete bronchial obstruction is obtained by a special type of cannula through which gas samples may be drawn from below the obstructed portion of the lung. With the first method the pulmonary changes are followed by Roentgen ray and fluoroscopy, the chest being intact. By the second technique the chest is wide open, allowing direct observation of the lungs through an "oscillating negative pressure box" which closely simulates the physiologic condition of a closed thorax. In the second and third papers of this series, to follow, we shall describe the results and theoretical and practical conclusions arrived at with the aid of these methods, described below.

Technique. In previous papers we showed that atelectasis can be constantly produced experimentally if a bronchus is obstructed in

an air-tight manner. For this purpose we elaborated a specially constructed one-way valve elastic balloon, which was introduced by the bronchoscope into a chosen bronchus of the dog. This balloon (Fig. 1), described elsewhere,¹⁰ can be inflated from the outside and then detached from its connection and left in place. Ten to 15 hours later roentgenographic examination of the animal, placed on a special stand for obtaining symmetrical pictures, shows the characteristic pictures of atelectasis with the displacement of the heart, the trachea and the diaphragm to the affected side and opacity of the affected lung. We believe that if we were able to produce atelectasis regularly it was because we used as an obstructive agent an elastic balloon and not a solid plug of cork, wood or

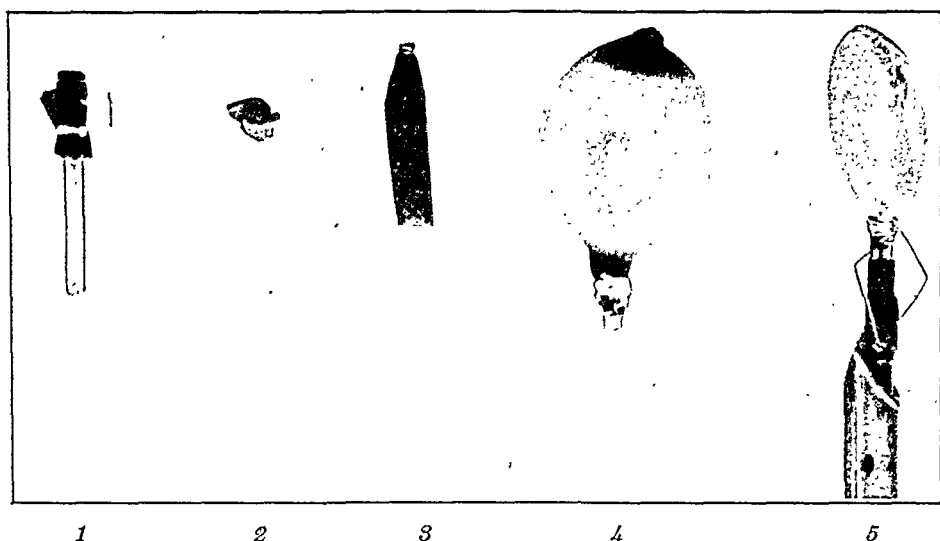


FIG. 1.—The balloon used for the obstruction of a bronchus in an air-tight manner. 1, A glass tube, 4 cm. long and a little less than 0.5 cm. across. Over its distal end a piece of old rubber glove, about 2 by 3 cm., has been placed with a double lateral twist and tied. A one-way valve in the direction of the arrow is thus formed. 2, End or head-on view of the valve, showing the lateral twists of the rubber in the formation of the valve. 3, A piece of rubber Kollman tubing, about 4 cm. long, into which the glass and valve are introduced. 4, The rubber tubing has been tied in an air-tight manner around the glass tube, 1 cm. from its proximal end, "E," and air has been inflated at this end which is open. The balloon is over-inflated to show the perfectly competent valve shimmering through the transparent balloon. 5, The completed balloon, which has an outer protecting cover of organic material, is depicted as having been previously introduced into the desired bronchus in the deflated state. It is now blown and ready to be detached and left in the bronchus. The reader should refer to *Archives of Surgery* (1928, 16, 528) for exact details.

metal, such as that tried by others before and after our investigations. We are convinced that with solid bodies it is almost impossible completely to obstruct a bronchus which yields and the diameter of which changes constantly with expiration and inspiration.

The solution of our present problem, however, required a new technique. We had to devise an instrument that would enable us to obstruct a bronchus completely, through the bronchoscope—in order to avoid opening of the chest or trachea. We must also be

able to draw alveolar air from below the obstruction for determination of gas percentages and intrapulmonary pressure. After a number of trials we constructed two types of apparatus, which gave us full satisfaction.

Intrabronchial Cannulas. The first apparatus is composed of two thin-walled brass tubes of 1 and 2 mm. internal diameter, respectively, and 50 cm. long. The external diameter of both tubes soldered together does not exceed 6 to 7 mm., so that the instrument easily passes through Jackson's full lumen 9-mm. bronchoscope. The narrow tube terminates 15 mm. proximal to the larger one, which is longer and has around its free end a wire crown to avoid obstruction by bronchial mucosa. For the same reason small lateral openings are made around this end. Above and below the distal opening of the small tube two brass rings are soldered around it, each of them bearing a groove for tying the small rubber balloon. Several models with more or less important modifications were made. In Fig. 2 1'-1 shows a bronchial catheter

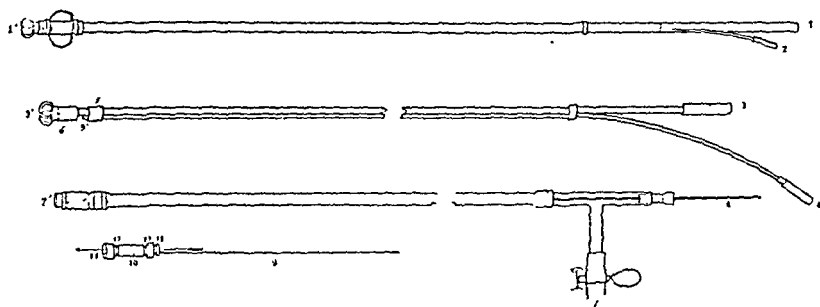


FIG. 2.—Intrabronchial catheters of Coryllos and Birnbaum. Model 1-1' is composed of a large external metal tube (5 mm. in diameter) which terminates in a free end surrounded by a crown (1') in order to avoid closure of this end by bronchial mucosa. A smaller tube passes into this tube and emerges 15 mm. from its distal end (1'), where it is soldered, so that there is no connection between Tubes 1 and 2. Around the distal end of the small tube is tied a piece of Kollman rubber tube, so that when air or fluid is introduced through 2 the rubber is distended, forming an obstructing balloon, as outlined. 3-3' is the model described in the text, showing 3-3', the larger bronchial tube, and 4-4', the smaller one, which serves for the inflation of the obstructing balloon which is not depicted in the diagram. 7-8 is the latest model; it is more detailed but is not essentially different from the preceding ones.

in which the small brass tube passes inside the larger tube throughout its length and emerges near its distal end, where it is filed down level with the outside tube, to which it is carefully soldered. Models 7 and 11 are the latest modification. A piece of fine India rubber tube (the tubing used for Kollman's urethral dilator is excellent) is put over the distal end of the cannula and securely tied around the groove with fine silk thread. This rubber tube is inflated through the small metal tube after the instrument is introduced into the chosen bronchus and forms an obstructing balloon. The

accurate inflation of the balloon is one of the most important points of the technique. It must be sufficient to obstruct the bronchus completely but not so excessive as to interfere with the circulation or innervation of the bronchus or with the ventilation of the other bronchi by displacement of the interbronchial spur or carina. These requirements are imperative, since, as a rule, these experiments last for many hours. It is necessary to know at all times whether the degree of inflation and obstruction remains unchanged. For this reason we devised a closed mercury manometer system

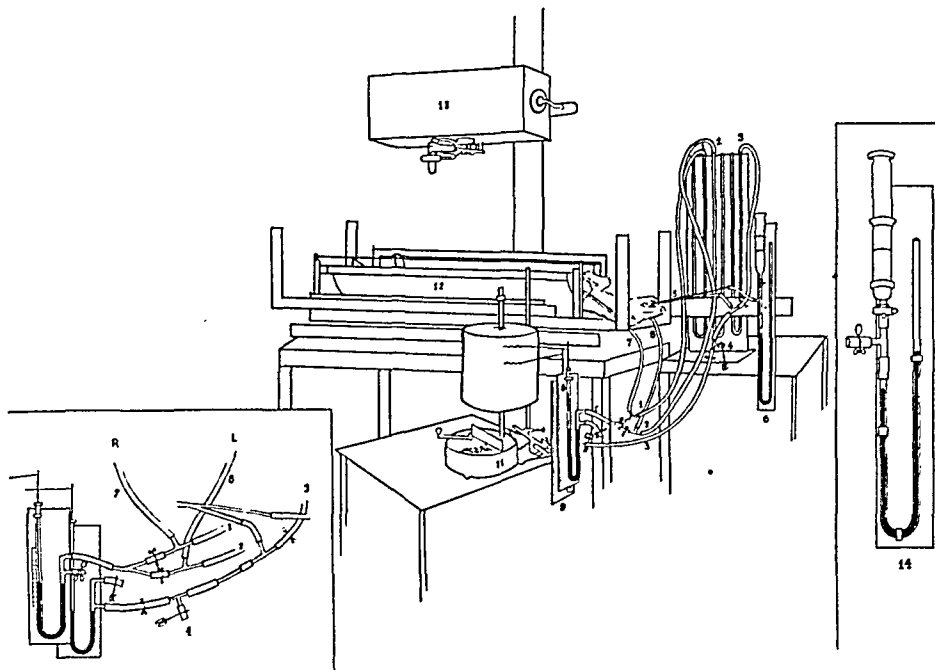


FIG. 3.—Lay-out of closed chest experiment. The animal is placed on our special Roentgen ray stand (12) and the bronchus blocked by means of the intrabronchial catheter (5) connected to the mercury manometer (6) (enclosure 14), which allows checking up its degree of inflation. In each pleural cavity a cannula is placed connected to rubber tubes 7 and 8. These tubes are connected (left enclosure) by *T* tubes to water manometers (1 and 2) and through another tube to a recording mercury manometer, so that it is possible to record on the smoked drum the tracing of the left or right pleural cavity pressure. The large bronchial tube of the bronchial catheter is connected by a *T* tube to a water manometer (3) and to a mercury manometer recording on the same smoked drum (11). A *T* tube was interposed in the latter rubber tube (4, left enclosure), allowing the taking of air specimens of intrapulmonary air for gas analysis. 13 is the adjustable fluoroscope or Roentgen ray unit.

(Fig. 3, 14), the free end of which was connected by way of a *T* tube to a syringe of 30 cc. capacity. The horizontal tube was connected through a rubber tube to the small tube of the bronchial catheter. By pushing down the plunger of the syringe, already filled with water, we could inflate the balloon to a size a little greater than the estimated diameter of the bronchus on which bronchoscopy had previously been done, and a marker was placed at the height of the

mercury meniscus in the closed end of the manometer. The bronchial catheter would then be disconnected. After it was introduced through the bronchoscope into the chosen bronchus it would again be connected with the manometer and the plunger of the syringe pushed in to distend the balloon and bring the mercury meniscus slightly above the previously placed marker. As long as the mercury stood at this level we were certain that the balloon was inflated.

Two types of experiments were carried out.

I. CLOSED-CHEST METHOD. In the first group, which will be designated by "closed-chest method" (Fig. 3), the animal, under iso-amyl-ethyl barbituric anesthesia, was placed on the Roentgen ray stand (12) so that the evolution of the experiment could be watched by fluoroscopy and Roentgen ray pictures. The intrapleural pressures during the experiment were taken by two water manometers (1, 2) connected with two cannulas introduced into the pleural cavities of the animal. Through the bronchoscope the pulmonary cannula was introduced and the balloon inflated, as already described. The larger tube of the bronchial catheter, which communicated with entrapped pulmonary air, was connected to a water manometer (3), to a recording mercury manometer and at times through a *T* tube (4) to the sampling bulb for analysis of specimens of alveolar air by a modified Henderson-Bailey gas analyzer. In this way it has been possible to follow simultaneously the intrapleural pressures and to record them on a smoked drum (11), to read and record the intrapulmonary pressure in the obstructed lung, to follow the changes in percentage of the entrapped alveolar air and to check up by fluoroscopy and roentgenographic examination the progress of atelectasis. At the same time the closed mercury manometer connected with the small tube of the intrabronchial catheter enabled us to know exactly the degree of inflation of the obstructing balloon.

II. OPEN-CHEST METHOD. The animal was anesthetized with sodium iso-amyl-ethyl barbiturate, 55 mg. per kilogram intraperitoneally. The neck was then shaved, the anterior wall of the chest prepared and intratracheal insufflation through the bronchoscope started. The thorax was then opened by hemisection of the sternum and a Balfour retractor was applied to maintain both thoracic cavities wide open. In the meantime (Fig. 4) a rotating valve (8) was connected with the suction faucet (10) and the number of its revolutions per minute regulated to the respiratory rate of the animal as it was before opening of the chest. The intrapleural pressure was taken before operation and the oscillations of negative pressure in the box (indicated in the water manometer, 9) were regulated so as to be equal to the intrapleural pressure of the animal before opening of the chest. The animal was then transported to the box and its head passed rapidly through the circular

opening of it. During this short time intratracheal insufflation was discontinued without any evil effect. The cover was tightly applied and the rubber collar fixed around the neck of the animal, smeared with petrolatum and secured by a gauze bandage or by a pneumatic collar, a later modification. Care was taken not to exert any unnecessary constriction around the neck. From now on the intratracheal insufflation can stop and the animal will

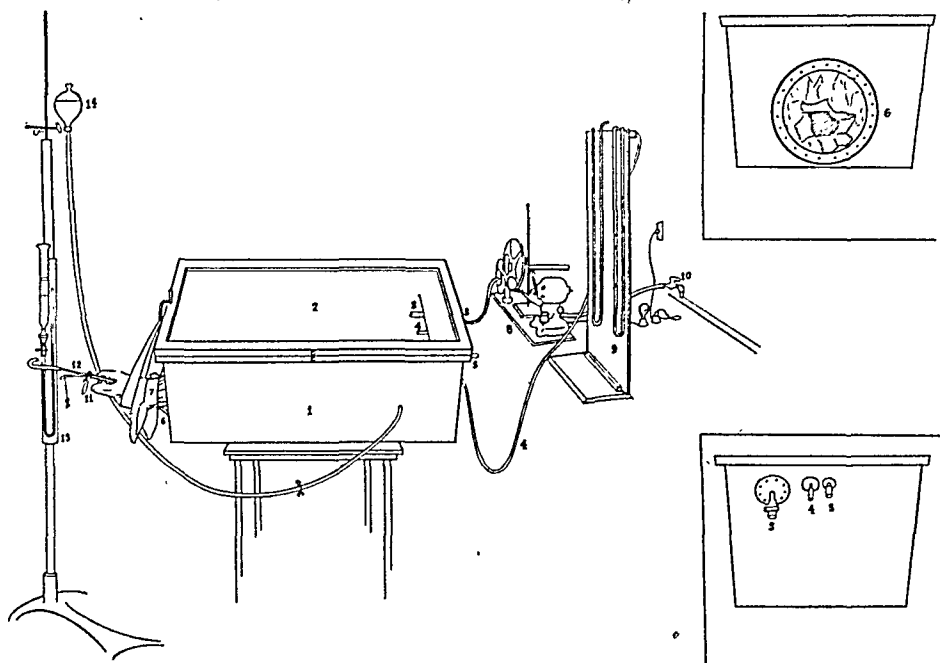


FIG. 4.—Lay-out of the open chest experiment in the oscillating vacuum box. After the chest is opened the animal is placed in the air-tight box (1), the cover of which (2) is made of plate glass. The head of the animal protrudes through the opening in the box (upper right corner enclosure 6, and also Fig. 6), around which is fixed an inflatable rubber collar which fits snugly around the shaved and petrolatum-anointed neck of the animal. The rotating valve (8), interspersed between the suction apparatus (10) and the box inlet (3), insures an oscillating vacuum in the box. This pressure is measured by the water manometer (9) and is equal to the negative intrapleural pressure of the animal taken previous to the operation. Inlet 5 serves to regulate the pressure in the box. A rubber tube passes through one wall of the box and may be connected to a reservoir with physiologic solution of sodium chlorid; by this means fluids can be administered under the skin or into the peritoneum of the animal during the experiment. Through the bronchoscope (11) the bronchial cannula is introduced into the left stem bronchus, and the balloon which is to occlude the bronchus is then inflated by means of the syringe-mercury manometer arrangement described in Fig. 3. The large tube of the cannula, in communication with the entrapped intrapulmonary air, is closed off unless samples of air are to be withdrawn through it for gas analysis.

breathe with its chest wide open at the same rate and with the lungs under the same negative pressure as in the closed-chest. Moisture and temperature inside of the box were kept as near normal as possible. Fig. 5 is a photograph of the layout of the whole experiment. It has been repeatedly possible to keep the animal in fine condition in the box for from 8 to 15 hours. A small tube was

provided for, through which saline solution, cardiotonics, or additional anesthetics could be given subcutaneously, if necessary, without disturbing the experiment. The pulmonary cannula was then introduced as for the "closed-chest" method.

We wish to point out that this box is based on a different principle from the differential pressure chamber of Sauerbruch. In the latter, only one pleural cavity being open, the steady and non-oscillating differential pressure (hypo or hyper) serves to keep the lung of the opened half-chest distended while the other lung breathes normally. In our box (Fig. 5), on the contrary, both pleural cavities being widely opened, no respiration can take place unless

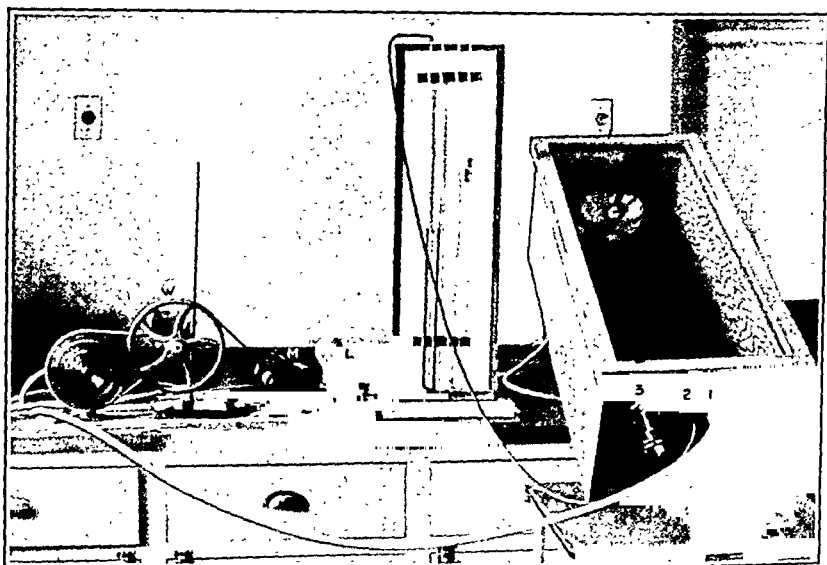


FIG. 5.—Box for oscillating vacuum. 1, 2 and 3 are outlets corresponding to 3, 4 and 5 of Fig. 4. *V*, rotating valve; *W*, speed-reducing wheel; *L*, 40-watt lamp resistance and *C* the cylindric collar, for the neck of the animal, which has lately been replaced by the inflatable rubber collar shown in Fig. 6.

there is an oscillation in the negative pressure box. It is in an airtight wooden structure, measuring 33 inches (83.17 cm.) in length, 14 inches (35.48 cm.) in width and 12 inches (30.48 cm.) in height; it is covered by a glass top which runs in a groove in the frame and thus permits the box to be closed hermetically. The groove is filled with mercury or, more conveniently, with petrolatum, so that a perfect seal is obtained. The box has three outlets; two of them are 1.3 cm. in diameter and the third, 0.3 cm. The first outlet is connected with the rotating valve (*V*) which produces an oscillating vacuum. The valve is rotated slowly by a two-pulley speed-reducing mechanism, consisting of a wheel (*W*) and a motor (*M*) with a rheostat installed. An extra 40-watt lamp resistance (*L*) in the system further reduces the speed of rotation.

The valve can be regulated to perform the necessary number of revolutions a minute to make the vacuum interruptions equal to the respiratory rate before the chest was opened. The rotating valve is connected at one end with an ordinary suction apparatus or the laboratory suction faucet. The other end of the rotating valve connects directly with the box (outlet 1). The second tube (2) is connected with a water manometer. The third tube (3), covered with a piece of rubber tubing and stopcock, connects the box with the outside air, regulating the degree of vacuum in it and allows the introduction of a thermometer. At the opposite panel of the box is a circular opening bearing a cylindrical collar (C) of

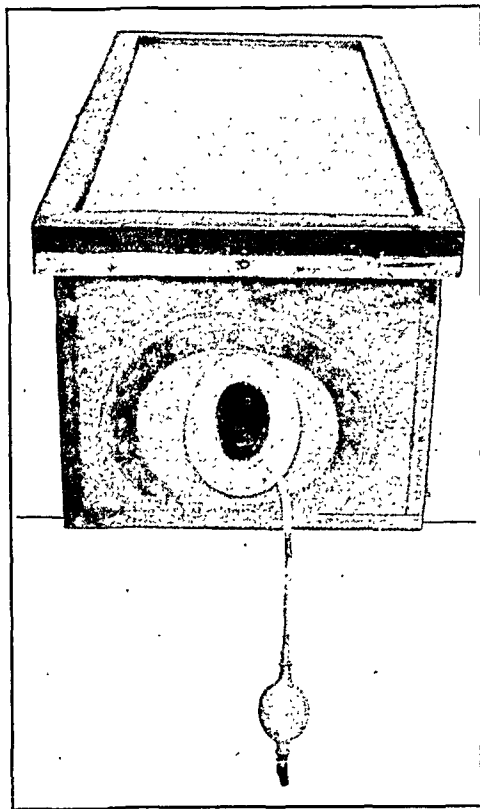


FIG. 6.—The inflatable rubber collar of the vacuum box, which fits in an air-tight manner around the previously shaved and petrolatum-anointed neck of the animal.

soft rubber tissue which can be adjusted around the shaved neck of the dog and fixed with a bandage so as to be air-tight. (More recently we have replaced this collar by a rubber collar which can be inflated with air.) (Fig. 6.)

By the methods described we have studied the absorption rates of different gases by the lung. These are described in a paper to follow. Using this technique it soon occurred to us that after the bronchial catheter was in place and a lobe of lung occluded, atelectasis could be expedited by mechanically withdrawing all the air or gas from it with a syringe and then washing out the lobe by

successively (6 or 7 times) introducing and withdrawing several hundred cubic centimeters of fresh oxygen each time, the lobe finally being left collapsed. Now the bronchial cannula is clamped off and the remnants of gases left to absorb until atelectasis occurs—a question of only minutes. “Washing out” with carbon dioxid gives an even more rapid atelectasis. The lobe is now ready for the introduction of the desired volume of gas or gases.

Summary. Two new methods are described which allow a physiologic study of the gas exchanges in a lobe or a whole lung after its bronchus has been completely obstructed.

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STUDIES IN PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION.*†

II. THE BEHAVIOR AND ABSORPTION TIMES OF OXYGEN, CARBON DIOXID, NITROGEN, HYDROGEN, HELIUM, ETHYLENE, NITROUS OXID, ETHYL CHLORID, AND ETHER IN THE LUNG.

WITH SOME OBSERVATIONS ON PLEURAL ABSORPTION OF GASES.

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THE phenomena of gas exchanges through a moist and living membrane such as the alveolar endothelium of the lung are quite

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† For complete bibliographies the reader should refer to the third article of this series and to previous papers of the authors.

different from those attendant upon simple physical diffusion of a gas through a porous cup. There is physical and physiologic evidence that they are dependent not only upon the speed of diffusion of a particular gas through space and its partial pressures or concentration on opposite sides of the wet semipermeable membrane but also upon its solubility and furthermore, in the lung, upon the integrity of the endothelium and of the intrapulmonary circulation. The alveolar air is separated from the venous blood by the endothelium of the air sacs and of the capillary vessels which cover their external surface and by a negligible amount of smooth and of extremely thin elastic fibers in the walls of the alveolus. Through this respiratory membrane the exchange of gases takes place.

Solubility of Gases in Fluids. When we regard the lung endothelium as a moist membrane we must consider gas exchanges as related to their solubility in it. This does not mean that the endothelium may be regarded as merely a layer of fluid, but the solubility coefficient of different gases in water gives some comparative basis upon which to formulate absorption times. Moreover, solubility of a gas is dependent upon the nature of the gas, those which are more basic or acid being more soluble than the neutral ones.* For example, carbon dioxid is much more soluble than hydrogen. The volumes of hydrogen, oxygen, carbon dioxid and nitrogen soluble in 1 cc. of water at body temperature are: Hydrogen, 0.016; oxygen, 0.024; carbon dioxid, 0.592; nitrogen, 0.016. In a mixture of gases the amount of each individual gas dissolved in a fluid is proportional to its partial pressure (Dalton's law). When a definite volume of liquid is saturated with a gas at constant temperature and pressure, an equilibrium is established between the gas in solution and that over the solution.

Diffusion of Gases Within the Alveoli and Through the Pulmonary Endothelium. With a mixture of gases in the alveoli the molecules of a particular gas diffuse through the alveolar space in all directions toward the alveolar endothelium at a rate inversely proportional to the square root of the density of the gas. The velocity of gas molecules is very great. For example, when hydrogen and oxygen are in a mixture the hydrogen molecule travels 1840 meters per second and the oxygen molecule travels 460 meters per second, for the oxygen molecule is 16 times as heavy as hydrogen ($\frac{1}{\text{square root of } 16} = \frac{1}{4}$). Alveolar air contains approximately 15 per cent oxygen and 80 per cent nitrogen under atmospheric pressure; thus 100 cc. of alveolar air would contain 15 cc. of oxygen and 80 cc. of nitrogen the mixture being under a pressure of one atmosphere. Since equal volumes of gases under the same pressures contain equal numbers of molecules, there are 80/15 as many nitrogen

* For the physicochemical aspect of the question see Getman's *Outlines of Theoretical Chemistry*, 4th ed., New York, John Wiley & Sons, 1928.

molecules as oxygen molecules in the alveolar air. It is evident, therefore, that if nitrogen and oxygen were of equal density, diffusibility and solubility in the alveolar endothelium and peri-alveolar blood, the number of molecules of nitrogen absorbed would be 80/15 as great as for oxygen. Actually we know this is not so, even though the density of nitrogen is almost equal to that of oxygen, oxygen diffusing into the blood much more rapidly than nitrogen which is only soluble to the extent of about 1 per cent in the blood. This is due to the fact that the velocity of diffusion through a moist membrane is not only inversely proportional to the square root of its density, as we have previously said, but also that it is proportional to the coefficient of solubility of the gas in the fluid concerned. That is why the speed of diffusion of carbon dioxid through a wet membrane is 30 times greater than for oxygen, although its density is greater. This can be easily shown by tying shut a frog's lung filled with oxygen or atmospheric air and placing it in an atmosphere of carbon dioxid (Loewy and Luntz). Very rapidly the lung is distended, owing to the diffusion of carbon dioxid into it, for the coefficient of solubility of carbon dioxid is 30 times greater than that of oxygen.

Oxygen and carbon dioxid are not merely dissolved in the plasma of the blood. The bulk of oxygen and carbon dioxid is in chemical combination in the blood. The first combines with hemoglobin, the second with alkali.

The Dissociation Curve of Hemoglobin in Relation to Respiration. The oxygen-hemoglobin compound has the property of dissociating with a fall in the partial pressure of oxygen; this dissociation is complete when the oxygen pressure is reduced to zero. In this way oxyhemoglobin represents an oxygen reserve in the red cells which maintains constant the amount of oxygen dissolved in the plasma, the latter representing the vapor tension of oxygen above the unstable oxygen hemoglobin compound.

Besides the partial pressure of oxygen in the alveolar air or tissues, another important factor in the dissociation of oxyhemoglobin is carbon dioxid. Increase in carbon dioxid hastens the dissociation of oxygen; it "shifts the dissociation curve of oxyhemoglobin to the right" and thus facilitates the unloading of oxygen into the tissues as the carbon dioxid in the blood increases. Although this is strictly correct, it is, according to Haldane,² of much less importance than the shifting of the carbon dioxid absorption curve in consequence of the reduction of hemoglobin.

In fact, decrease of oxygen in the blood and hemoglobin unsaturation increase the capacity of the blood for carbon dioxid, probably because reduced hemoglobin is a more alkaline substance than oxygen-saturated hemoglobin. The latter acting as a weak acid keeps carbon dioxid out of combination with alkali. Whatever the cause of this action may be, it is certain that saturation of hemoglobin decreases the capacity of blood for carbon dioxid, the result being that with high oxygenation the partial pressure of car-

bon dioxid in the blood rises although its percentage remains the same. For this reason more carbon dioxid is given off by the blood when its oxygen saturation is high (Werigo,³ Bohr, Hasselbach and Krogh⁴). Now it follows that if one lung is ventilated with a neutral gas as hydrogen, and the other with air, the latter will give off nearly 50 per cent more carbon dioxid than the former. (Haldane.)

Decrease in carbon dioxid has another important result, discovered by Bohr⁵ (1904) and called the "Bohr effect." Such a decrease shifts the dissociation curve of hemoglobin to the left so that whereas in the venous blood (carbon dioxid, 45 mm. of mercury; oxygen, 40 mm. of mercury) the hemoglobin is 68 per cent saturated, if carbon dioxid falls to 10 mm. of mercury the hemoglobin (without any increase in the oxygen pressure) becomes 85 per cent saturated. Furthermore, the oxygen is more firmly held in combination with hemoglobin so that notwithstanding this apparent increase in oxygen pressure and absence of cyanosis, the oxygen available to the tissues is greatly diminished.

Oxygen and carbon dioxid in the alveoli are kept quite constant at about 15 and 5 per cent, in spite of a constant interplay of gases through the alveolar endothelium. The inspiratory draft of air carries oxygen down only to a certain level in the bronchial tree; from this level oxygen, at a higher partial pressure, diffuses down through the larger and smaller bronchi and finally into the alveolar sacs where oxygen is at a lower partial pressure due to its continuous absorption from the alveoli into the blood. Similarly, on expiration, carbon dioxid is carried out of the alveoli only into the medium size bronchi, and from there it diffuses toward the larger bronchi and trachea. The mechanical carriage of oxygen and carbon dioxid in and out of the lung in the respiratory air drafts is thus a limited process, which depends upon the diffusibility of these gases to carry oxygen into the alveoli and tissues, and carbon dioxid out of the tissues and alveoli into the external air. This is, briefly, part of the intricate mechanism which, as previously stated, regulates the percentages of alveolar oxygen and carbon dioxid with such nicety.

With a lobe, containing air or other of the gases studied, cut off from the outside air by complete bronchial occlusion, the same factors we have considered in previous paragraphs come into play to bring about a complete absorption of alveolar gases (and atelectasis). The exact mechanism we leave to a succeeding paper.⁶ In this paper we shall give some typical protocols, comment on the phenomena of gas exchanges when one or more gases are introduced into an occluded lobe, and summarize, as far as the present studies allow, the actual absorption times of a stated amount of gas by one lobe of the lung. For the exact technique the reader should refer to a previous paper.⁷

Changes in Entrapped Alveolar Air as Indicated by Successive Gas Analyses. The results obtained in closed as well as open chest experiments show that within 2 to 7 minutes after bronchial obstruc-

tion the oxygen percentage falls rapidly from 15 to 5 or 6 per cent. It remains at about these figures until complete disappearance of the alveolar air. (Table 1.)

TABLE 1.—CHANGES IN OXYGEN AND CARBON DIOXID PERCENTAGES AFTER OBSTRUCTION.*

Dog.	Time after obstruction.	Oxygen.	Carbon dioxide.	Comment.
466 . .	Before bronchial obstruction	14.20	4.80	
	5 min.	..	4.09	
	35 min.	2.09	4.12	Animal dyspneic and cyanotic.
	2 hrs. 50 min.	4.00	5.30	
	2 hrs. 20 min.	5.70	6.07	Animal breathes quietly.
475 . .	10 min.	3.90	6.40	
	25 min.	3.90	4.70	
	50 min.	16.70	3.09	Obstructing balloon broke.
482 . .	10 min.	6.10	6.20	
	25 min.	6.04	6.26	
	40 min.	6.57	6.49	
	55 min.	5.41	6.71	
	5 hrs. 15 min.	6.81	6.45	
	6 hrs. 15 min.	5.35	6.97	
	10 hrs. 15 min.	5.81	5.53	

* Only figures in which possibility of error in gas analysis was excluded are given in this table.

In animals in which gas analyses were performed until complete atelectasis occurred, the curves plotted for percentages of oxygen and carbon dioxide show that the percentages vary inversely. (Fig. 1.) It is thus seen that the entrapped alveolar air rapidly undergoes marked quantitative changes, the percentage of oxygen dropping and carbon dioxide rising so that their respective partial pressures tend to come into equilibrium with the corresponding gases of the venous blood. These changes occur in exactly the same way in animals as in man, as shown by Loewy and von Schroetter⁸ (1905).

The succession of events as observed in the open-chest experiment, with the lung normally breathing in air, is as follows: Immediately after successful obstruction "the lung stops breathing," whereas the normal lung increases in size. There is a slight inspiratory excursion in the occluded lung owing to the decrease of pressure (increased negative pressure) in the box during inspiration, but it is insignificant as compared to the wide respiratory movements of the other lung. Little by little the size of the occluded lung decreases as a whole, without a conspicuous change in its general shape, appearance or color. Gradually it sinks toward the costovertebral sinus, whereas the other lung increases in size so that the heart is manifestly displaced toward the obstructed lung. Except for a slight cyanotic hue, the obstructed lung does not show any other

change until its volume is markedly decreased (to about one-fifth or one-seventh its original size). Then there appear dark bluish-brown patches scattered all over its surface without any predilection for the hilus or peripheral portion of the lung, as van Allen and Adams⁹ reported. After the great mass of gas is absorbed atelectasis advances rapidly, and within approximately 1 hour is complete. Figs. 2 and 3 show histologic sections of atelectasis produced in open- and closed-chest experiments. Often small islands of slightly aerated light-colored parenchyma remain on the dark bluish-black atelectatic lung, the complete disappearance of which may take half an hour or more. This general picture was

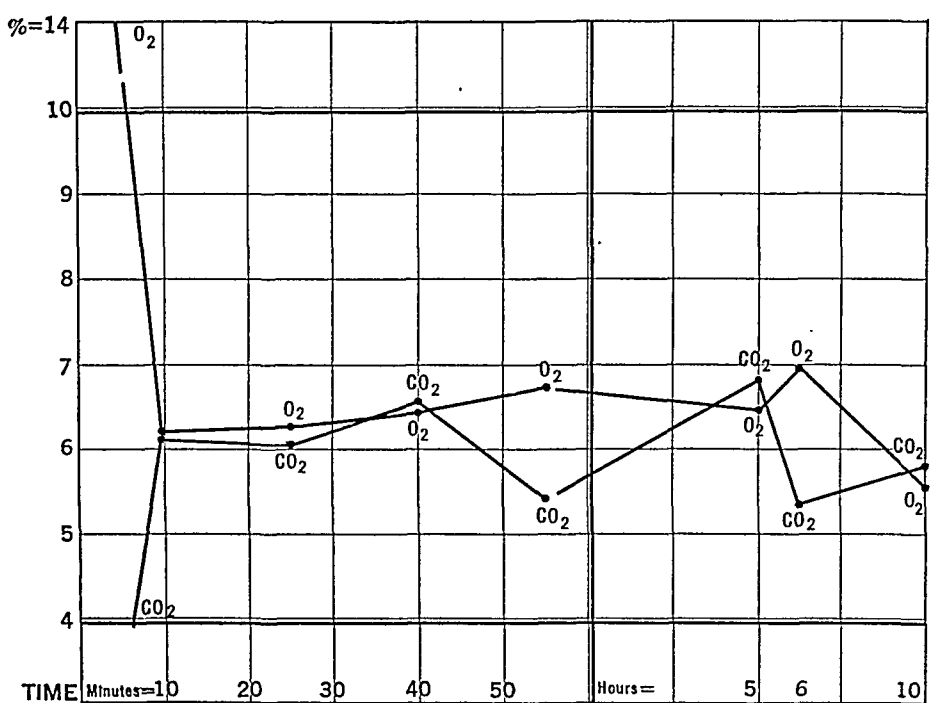


FIG. 1.—Graphic representation of percentages of oxygen and carbon dioxide obtained by alveolar gas analysis before obstruction and for a period of over 10 hours after obstruction. Dog. 482, March 30, 1930.

observed, as well, with gases other than air; only the time factor varied.

The actual volumes of gases introduced for the study of their absorption varied from 100 to 500 cc. of gas, depending for the most part upon the size of the animal. In the case of ether the pure vapor was obtained by slowly passing liquid ether through a metal coil immersed in water at 90° C., the coil in turn being directly connected to the lobe of lung under study through the pulmonary cannula. Ethyl chlorid was introduced directly in a spray from a standard commercial container through a long tube so that it reached the lung as a vapor. For the latter two vapors the volume

introduced was judged by the state of inflation of the lobe as compared to the inflation produced by measured volumes of gases previously introduced. The other gases were measured, as injected, with a P. A. Stoss-Nachfolger pneumothorax apparatus. The absorption times of a gas refer to the approximate period for absorption of gas in a lobe inflated to its full inspiratory state (for a given animal, to the same degree for each gas). It should be noted that the volumes of gas and their "absorption times" are given and not the "absorption rate." The actual "absorption rates" would have to be given in terms of cubic centimeters of gas per minute per square centimeter of absorbing surface of the lung at the particular time; this would be very difficult because the circulation and the area of the absorbing surface of a lobe are variable factors depending upon the particular state of inflation of the lung at any one moment. There are two opposing factors which normally regulate absorption. As the lung shrinks down the alveolar capillary circulation becomes progressively poorer as we have shown elsewhere,¹⁰ but the relative absorbing surface becomes greater per unit volume of contained gas, since the volume of an alveolus decreases relatively much more than its surface. (Fig. 4.)

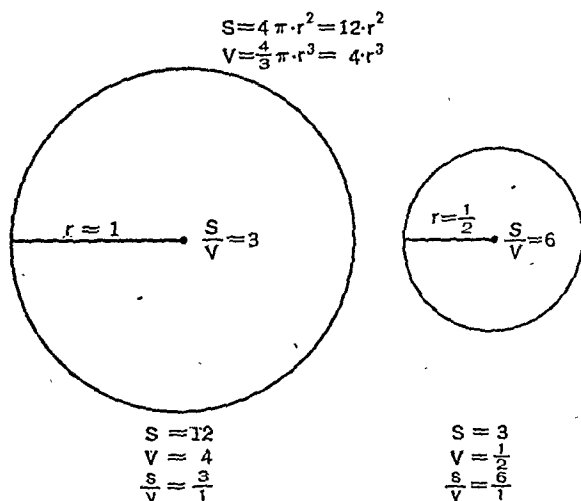


Fig. 4.—Showing the mathematic acceleration in absorption rate of gases in the alveoli of the lung. These relations probably hold true up to a point where the capillary circulation is definitely impaired.

Absorption of Oxygen and Carbon Dioxid. Closed-chest experiment. Dog 489. The experiment lasted $9\frac{1}{2}$ hours.

May 5, 1930. 11.45 P.M.: The rubber balloon on the cannula was introduced into the right lower bronchus.

11.52 P.M.: The balloon was blown up with 3 cc. of water.

11.54 P.M.: A sample of gas was obtained from the obstructed lung, 15 cc.; it contained 5.85 per cent carbon dioxid and 9.05 per cent oxygen.



FIG. 2.—Photomicrograph showing atelectasis produced in the open-chest experiment.

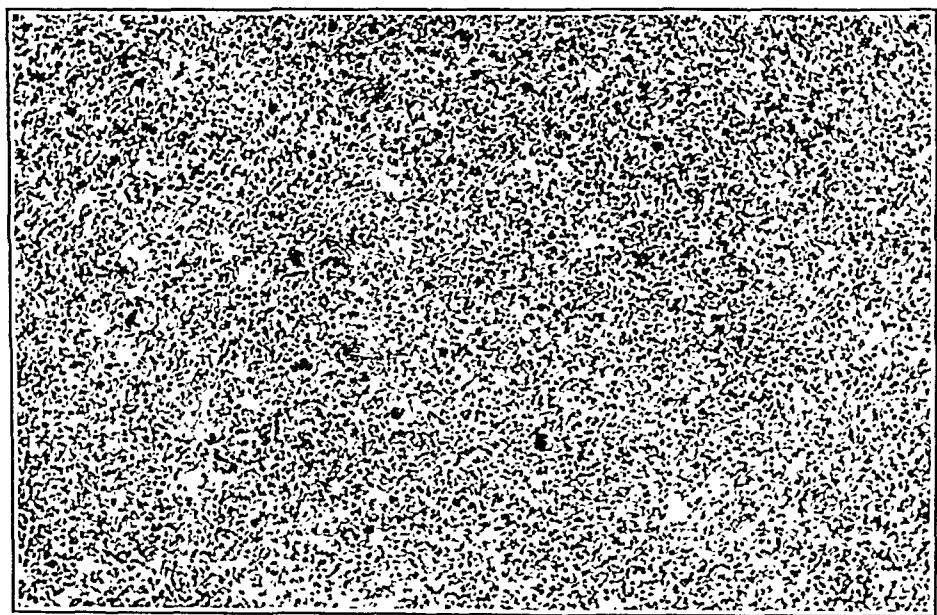


FIG. 3.—Photomicrograph showing atelectasis produced in the closed-chest experiment.



FIG. 5A



FIG. 5B

FIG 5.—Dog 511. *A* was taken after the introduction of 290 cc. CO_2 into the left lower lobe which appears distended. *B* was taken 10 minutes after the introduction of CO_2 into the left lower lobe. The gas has been completely absorbed.



FIG. 6.—Interstitial hemorrhage and edema in the left lower lobe after introduction of 100 per cent ether vapor into the lung previously rendered atelectatic (open chest experiment).



FIG. 7A



FIG. 7B

FIG. 7.—*A*, roentgenogram of a rabbit's chest after introduction of 75 cc. oxygen into the right pleural cavity. *B*, after complete absorption of gas from the pleura cavity; the heart has returned to its normal position.

12.03 A.M.: A sample of gas contained 5.98 per cent carbon dioxid and 6.66 per cent oxygen.

12.17 A.M.: A sample of gas contained 5.9 per cent carbon dioxid and 6.43 per cent oxygen.

12.28 A.M.: A sample of gas contained 6.1 per cent carbon dioxid and 7.36 per cent oxygen.

12.41 A.M.: A sample of gas contained 6.07 per cent carbon dioxid and 6.15 per cent oxygen.

12.52 A.M.: A sample of gas contained 6.05 per cent carbon dioxid and 6.02 per cent oxygen.

1.21 A.M.: Only 2 cc. of gas could be obtained.

1.35 A.M.: A roentgenogram showed a definite shift of the heart to the right.

1.53 A.M.: 100 cc. of oxygen was introduced into the obstructed lung. Roentgenograms taken 1 and 2 minutes later showed the heart shifted to the left.

1.58 A.M.: A sample of gas from the obstructed lung contained 6.94 per cent carbon dioxid and 51.2 per cent oxygen.

2.10 A.M.: A roentgenogram showed the heart again back to the right side.

2.15 A.M.: Only 4 cc. of gas could be obtained; this amount was insufficient for analysis.

2.22 A.M.: Fluoroscopy showed the heart a little more to the right than before the administration of oxygen. The respiration was very quiet.

3.50 A.M.: Fluoröscopy showed increased density of the right lower lobe.

5.26 A.M.: 100 cc. of carbon dioxid was introduced into the obstructed lung.

5.26½ A.M.: The heart was shifted to the left; the right lower lobe was clear.

5.30 A.M.: Only 4.8 cc. of gas could be obtained. It contained 54.16 per cent carbon dioxid.

5.32 A.M.: A roentgenogram showed the heart back again on the right; the breathing was very quiet.

6.25 A.M.: Fluoroscopy showed no further change; the right side of the diaphragm was immobile, and the heart moved toward the right on inspiration. There was no ventilation in the obstructed lung.

9.15 A.M.: A roentgenogram showed no change. The animal was sacrificed with 30 cc. saturated solution of magnesium sulphate injected intravenously.

9.20 A.M.: Autopsy revealed atelectasis of the right lower and accessory lobes (confirmed by microscopic sections). (See Figs. 5A and 5B, Dog 511.)

Open-chest experiment. Dog. 498, 10 kg. The experiment lasted 14 hours; negative pressure was -4, -7.5 of water; oscillation rate, 14 per minute; temperature in the box, 40° C.

May 15, 1930. 11.35 A.M.: The left lung was obstructed.

1.07 P.M.: A sample of gas contained 6.09 per cent carbon dioxid and 4.74 per cent oxygen.

8.30 P.M.: Atelectasis was complete in 9 hours.*

10.40 P.M.: 100 cc. of oxygen was introduced to distend the left lower lobe.

10.50 P.M.: A sample of gas contained 8.59 per cent carbon dioxid; the oxygen percentage was beyond the limit of the apparatus.

* In these experiments we were able to know with certainty when atelectasis was complete by the characteristic dark bluish color of the lung; this was repeatedly verified by histologic sections.

11.00 P.M.: The left lower lobe was again atelectatic; all the gas was absorbed.

11.10 P.M.: 100 cc. of oxygen was introduced to distend the left lower lobe.

11.20 P.M.: The left lower lobe was again atelectatic; all gas was absorbed.

11.25 P.M.: 100 cc. of oxygen was introduced to distend the left lower lobe.

11.31 P.M.: The left lower lobe was much smaller; 100 cc. more of oxygen was introduced.

11.35 P.M.: A sample of gas contained 10.63 per cent carbon dioxid; the oxygen percentage was beyond the limit of the apparatus.

12.13 A.M.: 100 cc. of carbon dioxid was introduced to distend the left lower lobe.

12.14½ A.M.: All the carbon dioxid was absorbed; the lobe was again atelectatic.

12.16 A.M.: 100 cc. of oxygen was introduced to distend the left lower lobe again.

12.27 A.M.: The oxygen was completely absorbed; the lower left lobe was again atelectatic.

12.37 A.M.: 50 cc. of oxygen and 50 cc. of carbon dioxid was introduced to distend the lower left lobe.

12.41 A.M.: All the gas was absorbed; the lobe was again atelectatic.

1.02 A.M.: 150 cc. of 100 per cent ether vapor was introduced to distend the lower lobe.

1.03 A.M.: All the ether was absorbed; the lobe was atelectatic again.

1.09 A.M.: 100 cc. of nitrogen was introduced into the left lower lobe.

1.25 A.M.: The heart stopped beating; the lung was unchanged.

Summary. The absorption time for oxygen in this experiment averaged 15 minutes; for carbon dioxid, 1.5 minutes; for 100 per cent ether vapor, 1 minute.

TABLE 2.—ABSORPTION TIMES OF OXYGEN AND CARBON DIOXID INDIVIDUALLY INTRODUCED IN A LUNG PREVIOUSLY RENDERED ATELECTATIC.

Dog.	Oxygen.		Carbon dioxid.		Comment.
	Cc.	Absorption time, min.	Cc.	Absorption time, min.	
511 . .	150	15	290	5	Closed chest experiment; roentgenographic control; other gases besides oxygen and carbon dioxid were successively introduced.
	275	15	275	5	
	280	12	250	7	
507	100	2½	Open-chest experiment.
504	100	2	Open-chest experiment.
498 . .	100	10 and 11	100	1½	Open-chest experiment.
499 . .	275	13	300	3	Open-chest experiment.

The figures in Table 2 show that the absorption times of oxygen and carbon dioxid show a constancy which is in agreement with the physical laws of diffusion and solubility. These times, however, seem to vary according to the anatomic conditions of the alveolar endothelium. This supposition is made on the bases of findings in Dog 504, in the atelectatic lungs of which were successively intro-

duced in the following order: nitrous oxid, carbon dioxid, ethyl chlorid, ethylene, carbon dioxid, ethyl chlorid, carbon dioxid, ethylene, oxygen and ether vapor. Because of the lesions of pulmonary endothelium by the gases introduced in it, carbon dioxid at the first introduction was absorbed in 2 minutes; at the second introduction, in 21 minutes, and at the third introduction, in 1 hour and 22 minutes.

Nitrogen when introduced alone under atmospheric pressure into the atelectatic lung was absorbed within 16 hours in Dog. 517. When pure nitrogen or other neutral gases, as hydrogen or helium, are introduced into an atelectatic lung, gas analysis of the alveolar content shortly thereafter shows that oxygen and carbon dioxid are present in the same percentage as in the alveolar blood, that is, about 5 or 6 per cent each. At the same time under fluoroscopic examination we found that after introduction of nitrogen there is at first a slight expansion of the lung which could be explained as due to the more rapid diffusion of oxygen and carbon dioxid from the venous blood into the alveoli than of nitrogen into the blood. From these facts it can be deduced, that when after the introduction of pure nitrogen the oxygen and carbon dioxid have reached these figures the absorption of the alveolar gases from this point on should proceed at the same rate as if air were now present.

Results Following Introduction of Neutral Gases Separately into the Atelectatic Lung. Nitrogen, hydrogen and helium were the gases used in these experiments.

Dog 517. Closed-chest experiment. This animal weighed 11 kg. Sodium iso-amyl-ethyl barbituric anesthesia was used and the left lower lobe bronchus obstructed.

5.30 P.M.: The left lower lobe was atelectatic.

5.45 P.M.: 100 cc. of nitrogen was introduced.

9.35 P.M.: A specimen of gas contained 5.51 per cent oxygen and 7.34 per cent carbon dioxid.

9.40 A.M. (next day): The lung was again atelectatic, showing that *the nitrogen was completely absorbed in 16 hours.*

Dog 515. Closed-chest experiment. This dog weighed 12.5 kg. Sodium iso-amyl-ethyl barbituric anesthesia was used. The left bronchus was obstructed.

12.10 P.M.: The left lung was rendered atelectatic.

12.40 P.M.: 105 cc. of hydrogen was introduced.

4.30 P.M.: A specimen of alveolar air contained 6.16 per cent oxygen and 5.03 per cent carbon dioxid.

9.57 P.M.: A specimen of alveolar air contained 5.50 per cent oxygen and 6.38 per cent carbon dioxid.

6.00 A.M. (next day): Lung again atelectatic, showing that the absorption time for hydrogen was 18 hours.

Dog 510. Closed-chest experiment. This dog weighed 22 kg. Sodium iso-amyl-ethyl barbituric anesthesia was given. The left stem bronchus was obstructed.

8.30 A.M.: Atelectasis was complete. 175 cc. of pure helium was introduced into the left lung.

9.30 A.M.: Gas analysis showed 5.83 per cent oxygen and 9.34 per cent carbon dioxide.

1.00 P.M.: Gas analysis showed 5.34 per cent oxygen and 6.22 per cent carbon dioxide.

2.10 P.M.: Gas analysis showed 5.25 per cent oxygen and 6.64 per cent carbon dioxide.

4.30 P.M. (next day): Lung almost but not completely atelectatic in 26 hours.

TABLE 3.—EXCHANGE OF ALVEOLAR GASES AS SHOWN BY CARBON DIOXID AND OXYGEN DETERMINATIONS AFTER INTRODUCTION OF VARIOUS GASES INTO AN OBSTRUCTED LOBE OF THE LUNG.

Gas.	Dog.	1930, May.	Description.	Time.	CO ₂ , per cent.	O ₂ , per cent.
Helium	507	22	Open-chest experiment; left lower lobe washed out 9 times with oxygen and allowed to become atelectatic; 150 cc. of helium was introduced into it at	2.00 P.M. 2.10 P.M. 5.45 P.M.	4.54 5.03	2.66* 2.83*
Helium oxygen	510	23	Closed-chest experiment; left lower lobe was obstructed and allowed to become completely atelectatic; 200 cc. of a mixture of equal volumes of helium and oxygen was then introduced into it at	5.50 P.M. 8.00 P.M.	5.86	8.29
Helium	This lobe was now washed out 3 times with pure helium and 175 cc. of helium was introduced into it at	8.30 P.M. 9.30 P.M.	9.34	5.83
			The next day at	1.00 A.M. 2.10 A.M.	6.22 6.64	5.34 5.25
Hydrogen	515	27	Closed-chest experiment; left lower lobe was washed out 7 times with oxygen and allowed to become atelectatic; then 105 cc. of hydrogen was introduced into it at	12.40 P.M. 4.30 P.M. 9.57 P.M.	5.03 6.38	6.16 5.50
Nitrogen	517	27	Closed-chest experiment; left lower lobe was obstructed and washed out 3 times with nitrogen by aspiration and distending it with pure nitrogen after each aspiration; then 100 cc. of nitrogen was introduced into it at	5.45 P.M. 9.35 P.M.	7.34	5.51

* These are unusually low figures for alveolar oxygen, probably due to poor respiration and anoxemia.

Table 3 is a résumé of these experiments.

The foregoing experiments show that a short while after the introduction of neutral gases into the atelectatic lung oxygen and

carbon dioxid diffuse through the alveolar membrane from the venous blood so that these gases are present in the alveoli under the same partial pressures as in the blood, as previously mentioned.

When a mixture of equal parts of a neutral gas and oxygen or carbon dioxid is introduced into the atelectatic lung the same phenomenon of rapid establishment of gas equilibrium occurs.

Dog 510.

5.50 P.M.: 200 cc. of equal parts of helium and oxygen by volume were introduced into the atelectatic left lung.

7.20 P.M.: Gas analysis showed 5.86 per cent oxygen and 8.29 per cent carbon dioxid.

The same modifications in the percentages of alveolar gaseous content occur when active gases (oxygen, carbon dioxid) are introduced individually into the atelectatic lung.

Dog 498. *Open-chest experiment.* This dog weighed 6.5 kg. Sodium iso-amyl-ethyl barbituric anesthesia was used. The left bronchus was obstructed and rendered atelectatic.

10.40 P.M.: 100 cc. of oxygen was introduced into the atelectatic lower left lobe.

10.50 P.M.: Gas analysis showed 8.59 per cent oxygen and 8 per cent carbon dioxid.

If an acute pathologic alteration of the lung endothelium is produced so that the respiratory membrane loses its permeability or the capillaries are damaged atelectasis does not occur. This is shown in a remarkable way when ether in 100 per cent concentration is introduced into the atelectatic lung. Undiluted ether vapor can be rapidly absorbed (100 cc. in 1 minute), but more often it produces a hemorrhagic edema (Fig. 6) strictly limited to the obstructed portion of the lung. In these cases further introduction of gas in the lung, even of carbon dioxid, which is usually rapidly absorbed, is not followed by atelectasis. The lung has lost its functional ability for the exchange of gases through the alveolar and capillary endothelium. Production of atelectasis has become impossible. This fact is illustrated in experimental Dog 499 (open-chest), the protocol of which is given here.

Dog 499. This animal weighed 15 kg. 55 mg. of Sodium iso-amyl-ethyl barbituric per kilogram of body weight was given intraperitoneally.

April 30, 1930. 1.00 P.M.: The dog was in the oscillating negative pressure box (oscillations from -4 to -8). The oscillation rate was 14 per minute. The heart rate was 116. Temperature, 40° C. $\frac{1}{4}$ grain (16 mg.) of ephedrin sulphate was given hypodermically. The left lung was obstructed and washed out with oxygen.

4.15 P.M.: There was complete atelectasis of the entire left lung.

4.21 P.M.: Carbon dioxid was introduced to distend the left lung (about 300 cc.).

4.24 P.M.: The carbon dioxid was completely absorbed and there was total atelectasis again.

4.41 P.M.: 100 per cent ether vapor was introduced to distend the lung to the size previously obtained with carbon dioxide (ether vapor was obtained by slowly passing liquid ether through a long metallic coil immersed in water at 90° C.).

4.45 P.M.: The left lung became edematous, of a dark pink to red color and larger than the atelectatic lung was at 4.24 P.M.

4.47 P.M.: Oxygen was introduced into the left lung to distend it to its former size.

5.02 P.M.: There was no apparent absorption; the volume of the lung was the same.

5.06 P.M.: The clamp on the lung catheter was removed. A strong odor of ether came out of the catheter in a forceful stream of gas; the whole amount of oxygen introduced was withdrawn, showing that none of the oxygen and not all of the ether had been absorbed.

Postmortem. The left lung was pinkish red; in section it was very hemorrhagic and edematous. The weight of the right lung was 140 gm.; of the left (edematous) lung, 232 gm. Microscopic section showed interstitial hemorrhage and edema.

Table 4 shows absorption times of ether in 2 experiments.

TABLE 4.—ETHER ABSORPTION TIMES.

Animal.	Weight, kg.	Volume, ether vapor.	Absorption time, min.
498	10	150	1
504	12	200	3

It is seen that 100 per cent ether vapor is quickly absorbed by the lung in each case, but often after the first introduction and always after a subsequent one it rapidly produces a hemorrhagic edema of the obstructed lobe, so that the lobe in question has lost its functional ability to absorb any gas or vapor which may be introduced into it from now on.

Tables 5 and 6 are summaries of a closed and open chest experiment, using various gases successively in a lower lobe.

TABLE 5.—ANIMAL 511. CLOSED-CHEST EXPERIMENT.

Gas.	Volume.	Absorption time, min.
Nitrous oxid	280	23
Oxygen	275	15
Ethylene	250	25
Oxygen	280	14
Carbon dioxide	275	5
Ethylene	275	15
Oxygen	275	12
Carbon dioxide	250	3
Nitrous oxid	250	17
Nitrous oxid	250	22

It will be noted that the absorption times in the open-chest run higher than for the closed-chest. This is probably due to the fact that fluoroscopic observation through the chest is not delicate enough to allow detection of the end point of absorption; that is,

after the great bulk of gas is absorbed further shrinkage of the lung and absorption of the minimal remnants cannot be followed by fluoroscope. (Figs. 3, 5A and 5B.) In the open-chest experiment absorption of the last traces of gas can be observed directly.

TABLE 6.—ANIMAL 504. OPEN-CHEST EXPERIMENT.

Gas.	Volume.	Absorption time, min.
Nitrous oxid	175	35
Carbon dioxid	175	17
Ethyl chlorid	175	10
Ethylene	175	29
Carbon dioxid	200	21
Ethyl chlorid	500	17
Carbon dioxid	300	42
Ethylene	300	13
Oxygen	300	19
Ether	200	3

From Table 5 it might appear that nitrous oxid and ethylene are innocuous to the pulmonary endothelium; even with repeated introduction their absorption times as well as those of oxygen and carbon dioxid are not prolonged. It should be remarked, however, that with nitrous oxid 5 cc. of serous fluid was obtained from the lobe of lung 11 minutes after its introduction and 1 cc. of serous fluid 22 minutes after its introduction. With ethylene 24 cc. of serous fluid could be withdrawn from lung $1\frac{1}{2}$ hours after introduction of the gas. This probably indicates the irritating effect of one or both gases. After the second introduction of ethylene 10 cc. of gas could still be withdrawn $2\frac{1}{2}$ hours after its introduction and yet fluoroscopy showed the appearance of the lung to be the same as at 15 minutes after introduction. It would appear then, that the great mass of ethylene (and also nitrous oxid) is absorbed quite readily, but that later with the lung almost atelectatic the absorption process is much slower, possibly due, for one thing, to a combination of impoverishment of capillary circulation in the collapsed state and, on the other hand, to a slight degree of endothelial damage. Considering the figures of the table, and that 100 per cent concentration of gases were used, it is likely that nitrous oxid and ethylene in concentrations usually used in anesthesia are fairly innocuous to the lung. The experiments cited for 100 per cent concentration of ether vapor show it to be much more irritating, hemorrhagic edema, as a rule, being produced, so that high concentrations of ether in anesthesia are to be particularly avoided. From Table 5 we saw that even assuming very slight endothelial damage, the successive absorption times for the great mass of gases were not materially lengthened by nitrous oxid and ethylene introduction. In Table 6 the first carbon dioxid introduction after the first nitrous oxid introduction was followed by atelectasis in 17 minutes, as compared to 3 to 5 minutes for carbon dioxid in Table 5. We

should probably deduce from Table 6 that nitrous oxid introduction was the cause of the lengthening of the carbon dioxid absorption time. However, Table 5 does show that *successive* introductions of ethylene and nitrous oxid did not prolong the absorption times of gases subsequently introduced. In Table 6 it is seen that the absorption times for carbon dioxid at successive introductions were relatively increased, being 17, 21 and 42 minutes respectively. Since the new factor introduced in Table 6 is ethyl chlorid, this may point to the deleterious effect of 100 per cent concentration of ethyl chlorid vapor on the endothelium. This effect does not appear to be permanent, for the larger second volume of ethylene following ethyl chlorid took only 29 minutes to absorb; later, ethylene following the second ethyl chlorid introduction took only 13 minutes, possibly because of the beneficial effect of the intervening carbon dioxid introduction. That the ethyl chlorid effect is not permanent is shown by the fact that the final oxygen introduced took only 19 minutes to absorb, about the average normal period. On the contrary, the ether vapor effect appears to be permanent.

TABLE 7.—AVERAGES OF ABSORPTION TIMES OF GASES FROM A LUNG INFLATED TO FULL INSPIRATORY STATE.

Oxygen	15 min.	Nitrous oxid	17 to 35 min.
Carbon dioxid	4 "	Ethylene	13 to 29 "
Nitrogen	16 hrs.	Ethyl chlorid	10 to 17 "
Hydrogen	18 "	Ether	1 to 3 "
Helium, over	26 "		

For the sake of completeness, it is of interest to compare the absorption times of air, nitrogen, oxygen, carbon dioxid, hydrogen and helium in the pleural cavity, with those for the lung; for the pleura is a closed cavity completely lined with an endothelial membrane, permeable to gases, over half of which is in close relation to the capillary system of the lung. Therefore, it would not be surprising if gas absorption in the pleural cavity were accomplished according to the same laws which regulate gas absorption in an alveolus completely closed off by bronchial obstruction. This conception which will be elaborated in a forthcoming paper on gas behavior in the human pleura justifies the presentation of the data to follow.

Behavior of Gases in the Pleural Cavity. Some preliminary observations were carried out in rabbits, rather than the dog, for they have a mediastinum which is much more comparable to that in the human. The mediastinum of the dog is a flimsy structure which is permeable to gases and fluids so that a unilateral pneumothorax is not possible. On the contrary, in rabbits a measured volume of gas can be introduced into the pleural cavity of one side and unilateral pneumothorax produced. Its absorption is followed by observing the degree of return of the heart and mediastinum

back to their normal position as checked up by fluoroscopy and Roentgen ray. (Figs. 7A and 7B.)

The gases used were air, nitrogen, oxygen, carbon dioxid, hydrogen and helium. In each case 75 cc. were introduced into the pleural cavity of a rabbit weighing about 2 kg., and the absorption times studied by fluoroscopy and Roentgen ray. (Table 8.) This volume of gas produced a very marked shift of the heart to the opposite side. (Figs. 7A and 7B.) In 3 experiments carbon dioxid, oxygen and nitrogen were introduced into the pleura and samples of gas later removed for analysis of their carbon dioxid and oxygen contents. In this way some insight into the nature of gas exchanges through the pleura was to be had.

TABLE 8.—ABSORPTION TIMES OF GASES INTRODUCED INTO THE PLEURAL CAVITY OF RABBITS.

Gas.	June, 1930.	Rabbit.	Volume gas introduced, cc.	Pleural cavity.	Absorption time.
Air	4	18	75	Right	6 days
Nitrogen	4	14	75	Right	6 "
	16	16	75	Right	6 "
Oxygen	11	16	75	Left	2 hrs.* for 40 cc.
Carbon dioxid	11	14	75	Left	5 min.
Hydrogen	4	17	75	Right	4 days
Helium	4	16	75	Right	4 "
"	16	14	75	Right	4 "

* 35 cc. of gas were withdrawn for determination of carbon dioxid and oxygen percentages.

TABLE 9.—TRANSPLEURAL EXCHANGE OF GASES AS SHOWN BY CARBON DIOXID AND OXYGEN DETERMINATIONS AFTER INTRODUCTION OF VARIOUS GASES INTO THE PLEURAL CAVITY OF RABBITS.

Gas.	Rabbit	Date.	Description.	Time.	CO ₂ , per cent.	O ₂ , per cent.	N ₂ , per cent (by subtraction).
Carbon dioxid	19	May 1, 1931	75 cc. carbon dioxid in right pleural cavity at	11.00 A.M.			
			Gas sample at	11.06 A.M.	90.00	1.50	8.50
Oxygen	16	May 11, 1930	75 cc. oxygen in left pleural cavity at	2.40 P.M.			
			Gas sample at	3.00 P.M.	6.53	93.40	Trace
			Gas sample at	4.40 P.M.	6.52	93.44	Trace
Nitrogen	18	June 11, 1930	75 cc. nitrogen in left pleural cavity at	3.55 P.M.			
			Gas sample at	4.15 P.M.	4.67	3.67	91.66
			Gas sample next day at	8.30 P.M.	5.69	9.90	84.41

Table 8 is a summary of pleural absorption times. In the pleura, as in the lung, the times of absorption for the inert gases, nitrogen,

hydrogen, helium; and for air are relatively high, as in the lung, oxygen and carbon dioxid have comparatively short absorption times.

TABLE 10.—TRANSPLEURAL EXCHANGE OF GASES AS SHOWN BY CARBON DIOXID AND OXYGEN DETERMINATIONS AFTER INTRODUCTION OF CARBON DIOXID INTO THE PLEURAL CAVITY OF THE DOG.

Gas.	Dog.	Date.	Description.	Time after introduction.	CO ₂ per cent.	O, per cent.	N, per cent (by subtraction).
Carbon dioxid	671	May 9, 1931	250 cc. CO ₂ introduced into right pleural cavity at . .	11.50 A.M. 3 min. 15 min. 1 hr., 7 min. 2 hrs., 20 min.	96.00 69.4 10.9 6.4	1.5 10.2 15.2 14.1	2.5 20.4 73.9 79.5

TABLE 11.—SUMMARY OF SOLUBILITY COEFFICIENTS AND ABSORPTION TIMES OF VARIOUS GASES.

Gas.	Density, gm. per 1000 cc.	Molecular weight.	Solub., gm. per 100 gm. H ₂ O.	Temp.	Solub. coeff., cc. gas. sol. in 1 cc. H ₂ O.	Absorption time.	
						Pleura* (rabbit).	Lung† (dog).
Air	1.30	..	0.004	35° C.	0.015	6 days	16 hrs.
Nitrogen	1.25	28	0.003	35° C.	0.012	6 days	16 hrs.
Oxygen	1.43	32	0.007	35° C.	0.024	2 hrs.	15 min.
Carbon dioxid . .	1.98	44	0.330	35° C.	0.592	5 min.	4 "
Hydrogen	0.09	2	0.00025	35° C.	0.016	4 days	18 hrs.
Helium	0.18	4	0.00020	25° C.	0.014	4 "	26 "
Nitrous oxid . . .	1.95	44.20	0.067‡	37° C.	0.326	..	17 to 35 min.
Ethylene	1.27	28.03	0.010‡	37° C.	0.080	..	13 to 29 "
Ethyl chlorid vapor	2.86	64.50	0.878§	37° C.	3.07	..	10 to 17 "
Ether vapor . . .	3.11	74	4.962§	37° C.	15.94	..	1 to 3 "

* 75 cc. of gas introduced into pleural cavity.

† Enough gas to inflate one lobe to full inspiratory state.

‡ Volumetrically determined by us with the eudiometer.

§ Gravimetrically determined by us.

Gas Exchanges in the Pleura. In Table 9 the pleural gas exchanges following introduction of carbon dioxid, oxygen and nitrogen in the pleura of rabbits are given. When carbon dioxid was introduced into the pleura gas analysis 6 minutes later showed that 1.5 per cent O₂ and 8.5 per cent N₂ had diffused into the pleural cavity. Due to the very rapid absorption of CO₂ in the rabbit, analysis of the pleural gases over an appreciable period was found impossible. For this reason 250 cc. of CO₂ was introduced into the right pleural cavity of a dog weighing 10 kg. (Table 10.) Owing to the flimsy mediastinum of the dog, which is permeable to gases, a bilateral pneumothorax was thus produced, and 20-cc. samples of pleural gas were withdrawn for analysis over a period of 2 hours

and 20 minutes after introduction of carbon dioxid. Two hours and 45 minutes after introduction 55 cc. of gas could still be withdrawn from the right pleural cavity. Table 10 shows a progressive fall in CO_2 percentage and rise in O_2 and N_2 percentages, the last reading showing 6.4 per cent CO_2 , 14.1 per cent O_2 and 79.5 per cent N_2 , or approximately the composition of alveolar air or of the gases in arterial blood. We are as yet unable to state definitely the relative importance of the visceral and parietal pleura in the pleural exchange and final equilibrium of gases. This phase of the subject is still under investigation.

When oxygen was introduced into the pleura, analysis 20 minutes later showed a carbon dioxid percentage of 6.53 and an oxygen percentage of 93.4. Gas analysis 1 hour and 40 minutes later showed practically the same percentages. Carbon dioxid had therefore diffused into the pleural cavity and was present at about venous blood concentration. (Table 9.) Only traces of nitrogen had diffused into the pleural cavity. An equilibrium thus tended to be established; a perfect equilibrium is never obtainable so long as the absorbing power of the pleura is unimpaired. The constant imbalance and continuously changing partial pressures of gases or vapors on opposite sides of an absorbing membrane can account for this lack of equilibrium. Aside from this factor, in considering the rapidity of absorption and diffusion of gases through living membranes or tissues, an analogy is to be found *in vitro* in the diffusion of gases from one side of a membrane and through it into a stream of running water rather than into a beaker of water. A fresh stream of blood, arriving as it does in a relatively unsaturated state, is available to dissolve and continuously to carry away gases or vapors from the pleura or lung.

When nitrogen was introduced there was a diffusion of nitrogen out of, and oxygen and carbon dioxid into the pleural cavity. Gas analysis 20 minutes after the introduction of nitrogen showed that 4.67 per cent of carbon dioxid and 3.67 per cent oxygen had diffused into the pleural cavity. These percentages were obviously below equilibrium points because gas analyses 28 hours later showed carbon dioxid had risen to 5.69 and oxygen to 9.9. The latter figure for oxygen, which is between the venous oxygen concentration (5 per cent) and arterial concentration (14 per cent), may indicate that a further rise of oxygen percentage would have been found in subsequent analyses, or else that oxygen in the pleura now tended to be in equilibrium with arterial blood.

Pleural Absorption Compared to Pulmonary Absorption. From Table 11 it will be noted that in the pleura, as well as in the lung, air, nitrogen, hydrogen and helium require a long period for absorption compared to oxygen and carbon dioxid; for the former gases are dependent chiefly on their degree of solubility in the moist endothelium and blood for absorption from the lung. That the

density, and therefore diffusibility, has very little to do with the time of absorption of an inert gas, is clearly demonstrated in the case of nitrogen and hydrogen which are about equally soluble in water. Nitrogen with a molecular weight of 28 is 14 times as dense as hydrogen with a molecular weight of 2. Nitrogen, therefore, has only about $0.26 \left(\frac{1}{\sqrt{14}} \right)$ the diffusion speed of hydrogen and should, theoretically, require 4 times as long to absorb as does hydrogen; yet in the pleura nitrogen required only 1.5 times as long a period to absorb as did the hydrogen. In the lung, nitrogen and hydrogen were absorbed in approximately equal times. Although the solubility coefficients of oxygen and carbon dioxide are respectively 2 times and 50 times that of nitrogen (Tables 8 and 10), the former two gases were absorbed from the lung and pleura in far less than one-half and one-fiftieth the time for nitrogen. As previously mentioned in the case of oxygen and carbon dioxide, the factors of affinity of carbon dioxide for alkalies of the tissues and blood and of oxygen for hemoglobin account for rapid absorption of these gases as compared with nitrogen, hydrogen, helium and air. These factors appear to obtain both for the pleural cavity and the lung. Carbon dioxide is apparently quite as rapidly absorbed from the pleura as from the lung. Oxygen would appear to be slower in absorption from the pleura, and the inert gases, nitrogen, hydrogen, helium and air require considerably longer times for pleural absorption.

It would not, however, appear surprising for the pulmonary absorption of a gas to be more rapid than pleural absorption; in fact, it is rather to be expected. The construction of the lung is ideal for gas absorption, the myriads of alveoli offering a large absorbing surface (a maximum of 1000 square meters) for the gases contained within them. Each alveolus is surrounded by a rich capillary network in intimate contact with the very thin pulmonary endothelium through which a rapid interchange of gases can take place. As compared with the pulmonary endothelium the pleura offers a relatively small absorbing surface for the volume of gas introduced into the pleural cavity; it is not endowed with a highly specialized capillary network such as is found around each alveolus. It seems reasonable to deduce, therefore, that the most of the absorption is carried out by the visceral pleura, notwithstanding the lung's decrease in surface and the impaired circulation due to collapse of the underlying pulmonary tissue. This may be why the rate increases as the lung expands (improved pulmonary alveolar circulation) and decreases as the pleura thickens. On this important point studies on the human are being carried out at Metropolitan Hospital, Tuberculous Service, New York City.

In a general way Table 11 shows that both for gases and anesthetic vapors the absorption times for the lung are inversely proportional to the solubility coefficients of the gases and vapors studied. This

is shown by taking the solubility coefficient of nitrogen, an inert gas, as a standard, and comparing to it the solubility coefficient of the gas or vapor in question, remembering that the higher the solubility coefficient, the quicker is the absorption. Oxygen and even the highly soluble carbon dioxide are noticeable exceptions to the rule. The affinity of carbon dioxide for alkali of the tissues and blood and of oxygen for hemoglobin, already pointed out, account for the relatively rapid absorption of these gases from the pleural cavity and lung.

Ethylene required a much shorter time for absorption and ethyl chlorid vapor and helium a little longer time for absorption than calculated from the water solubility coefficients of these gases. Ether vapor was absorbed most rapidly of all, as would be expected from its high solubility coefficient, in spite of the fact that its diffusibility is least of all the vapors and gases studied (because of its high density); its absorption time is in agreement with the findings of Van Mechelen,¹¹ who showed ether to be absorbed from the human lung with great rapidity. He found that on inhalation of $1\frac{1}{2}$ liters of air containing from 9 to 26 per cent ether (26 to 78 gm. per 100 liters air) over 95 per cent of the ether was absorbed from the human lung in 2 seconds. Van Mechelen found that ether was in some instances considerably less soluble in blood than in distilled water. However, there are two other factors aside from the high solubility of ether which can account for the rapid absorption of ether from the lung. The first is that arterial blood (carotid artery) in a single and first passage through a lung containing about 14 per cent ether became two-thirds saturated with this anesthetic. The second point is that Van Mechelen showed the arterial blood to contain considerably more ether than the venous blood even after more than 3 hours of anesthesia. The venous blood thus remains relatively unsaturated by ether for long periods and so can absorb considerable volumes of ether vapor as it courses through the lung again and again. In the light of these considerations the rapid absorption of ether from the lung becomes clear.

A point of interest is the cause and mechanism of the possible irritant or even corrosive action of strong concentrations of ether vapor in the lung. As previously stated, 100 per cent concentration ether vapor often produced hemorrhagic edema of the lung in our experimental animals. A possible contributory cause of this may lie in the fact, as we have found, that ether containing traces of water may exist as a liquid at body temperature ($37^{\circ}\text{C}.$), whereas pure ether boils at $34.5^{\circ}\text{C}.$ and can exist only as a vapor at body temperature. Moreover when water is dissolved in ether to the extent of 9.92 to 100 gm. of ether (0.09 gm. H_2O per gm. ether) a perfect solution is obtained, which does not boil below $45^{\circ}\text{C}.$ Due to water vapor in the lung and water in the endothelium itself, it is conceivable, therefore, in view of what we have just said, that

ether in high concentrations in the lung may condense and remain as a liquid on the pulmonary endothelium. Such liquid ether might irritate pulmonary tissue first by its dehydration of the endothelium and then by a direct action upon it. This could account for the hemorrhagic edema produced by high concentrations of ether vapor in the lung.

Summary and Conclusions. Gases and anesthetic vapors contained in alveolar cavities shut off by complete bronchial obstruction gradually leave the lung and finally disappear so that the lung becomes atelectatic.

The speed of the disappearance of these gases is proportionate to their solubility coefficient, diffusion speed and to their chemical affinities for substances dissolved in the blood (hemoglobin in the case of oxygen, alkalies in the case of carbon dioxide, etc.).

Since ligation of the branches of the pulmonary artery corresponding to the obstructed lung prevent this disappearance of gases and vapors from the alveoli (Lichtheim, Schlaepfer), it has been concluded that this disappearance is due to absorption by the blood circulating through the lung. However, no direct evidence of this contention has ever been presented.

In this paper a detailed study has been presented of the times of absorption of oxygen, carbon dioxide, nitrogen, hydrogen and helium introduced into a lung previously rendered atelectatic. In this way the absorption times have been determined with considerable accuracy and their absorption has been proven.

Determinations which were carried out by the same technique for anesthetic vapors and gases, namely, ether, ethyl chlorid, nitrous oxide and ethylene showed the great rapidity of their absorption.

Integrity of the alveolar endothelium is just as necessary as integrity of the pulmonary circulation. Edema of the lung produced by injection of concentrated ether vapor into the lung instantaneously stops gas absorption.

Comparative study of absorption by the pleural cavity of oxygen, carbon dioxide, nitrogen, air, hydrogen and helium showed that their absorption is regulated by the same physicochemical laws governing absorption of gases from the obstructed lung.

On the basis of the above experimental findings it has been endeavored to justify our contention that atelectasis always follows complete bronchial obstruction and that it cannot occur without complete bronchial obstruction.

The aim of this investigation has been to offer a direct experimental proof that complete bronchial obstruction is the exclusive cause of atelectasis.

In the third paper of these series a new theory of production of atelectasis will be given.

NOTE.—We are indebted to Mrs. Aies Larsen for preparation of histologic sections, to Miss Helen C. Warny of the Airo-Balloon Company, New York City, for a supply of helium gas, and to Mr. Eugene Ostrow for technical assistance.

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STUDIES IN PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION.*

III. A THEORY OF AIR ABSORPTION IN ATELECTASIS.

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CONSIDERATIONS brought forth in the previous papers of this series lead us to the conclusion that atelectasis is the end result of the interchange between the gases of the alveoli and the perialveolar capillary blood through the pulmonary endothelium. Atelectasis must inevitably follow complete bronchial obstruction as a result of the absorption of the alveolar gases; conversely atelectasis cannot occur unless the alveolar gases are completely shut off from the external air. Incomplete obstruction of a bronchus would mean a renewal by the inspired air of the gases depleted in alveolar absorption.

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In the light of this theory atelectasis depends upon the difference in partial pressures of the gases on either side of this membrane, upon the integrity of the pulmonary endothelium and upon the integrity of the pulmonary circulation allowing the gases absorbed from the alveoli to be carried away from the lung by the blood.

The most important factor in the accomplishment and regulation of this exchange of gases is the difference in partial pressures of the gases in the alveoli and perialveolar capillary blood. Paul Bert showed first that in the alveoli or in the blood it is not the total pressure of the gas mixture, but the partial pressure of each individual gas acting as if it were alone which is of importance. In a

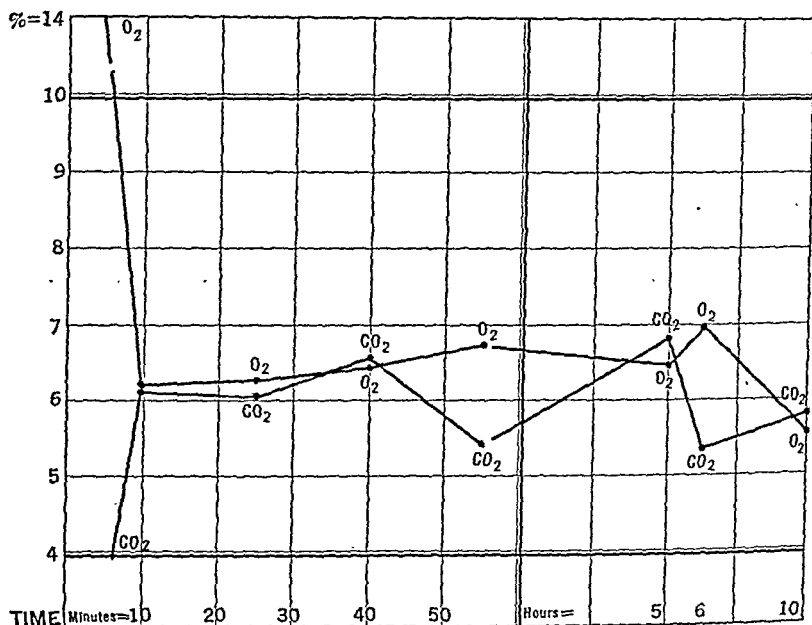


FIG. 1.—Graphic representation of percentages of oxygen and carbon dioxide obtained by alveolar gas analysis before obstruction and for a period of over 10 hours after obstruction of the right lung. Dog 482.

mixture of gases, where no chemical action occurs, each gas behaves independently; this fact is formulated in the law of partial pressures, of Dalton. Thus, if 100 cc. of oxygen and 400 cc. of nitrogen both at one atmosphere of pressure are mixed, the resulting mass of gas occupies 500 cc. at the same pressure. Since equal volumes of gases at the same pressure contain equal numbers of molecules, the mixture contains 4 times as many nitrogen as oxygen molecules in the contained space. This means the nitrogen can exert 4 times as much pressure against a given membrane, for the bombardment and number of its molecules against it is 4 times as great as oxygen. Thus the oxygen acts as if it were under a pressure of only $\frac{1}{5}$ of an

atmosphere ($\frac{1}{5} \times 760 = 152$ mm. Hg), while the nitrogen acts as if it were under a pressure of $\frac{4}{5}$ of an atmosphere ($\frac{4}{5} \times 760 = 608$ mm. Hg).

In Fig. 1 is shown the percentages of oxygen and carbon dioxide obtained by alveolar gas analysis before obstruction of a lobar bronchus and for a period of 10 hours thereafter. Within 10 minutes after obstruction the oxygen has fallen from 15 to 5 per cent and the carbon dioxide has gone from 5 to 6 per cent, showing that an approximate equilibrium with the venous alveolar capillaries has been established. From this point on, a series of gas exchanges takes place, leading ultimately, in 12 to 16 hours, to an atelectasis, as occurred in this case.

TABLE 1.—PERCENTAGES AND PARTIAL PRESSURES OF OXYGEN, CARBON DIOXIDE AND NITROGEN IN ALVEOLAR AIR AND VENOUS CAPILLARY BLOOD.

Gas.	Alveolar air.		Venous blood.	
	Per cent.	Partial, pressure mm. Hg.	Per cent. of one atmosp.	Partial pressure, mm. Hg.
Oxygen	15	114	5	38.0
Carbon dioxide	5	38	6	45.6
Nitrogen	80	608	..	608.0

Table 1 represents in round figures the percentages of one atmosphere and the corresponding partial pressures of gases in the alveolar and venous air. These differences in partial pressures are possible notwithstanding the continuous exchange of gases through the respiratory membranes, only because the alveolar air is continuously renewed by respiration, by drawing by diffusion on the tidal air filling the bronchi on each respiration. This exchange is so active that in spite of the continuous renewal of air the alveolar air is poorer in oxygen and richer in carbon dioxide than the atmospheric air. It is precisely these differences in partial pressures between alveolar and venous gases which render possible oxygenation of the venous blood and elimination of its carbon dioxide.

It is obvious then that if a bronchus is obstructed the air entrapped in the lung will undergo qualitative changes. Its composition will gradually approach the percentages of the gases of the venous blood which is constantly coursing around the alveoli, carrying away gases which are under excess pressure in the alveoli (oxygen) and giving off gases to the alveoli which it has in excess (carbon dioxide). Such qualitative changes necessarily result in quantitative changes.

In order to simplify the question, we shall graphically represent the alveolus by a circle surrounded by a larger circle which represents the venous blood circulating in the perialveolar capillaries. (Fig. 2.) Further, 100 will represent the volumes of the air content of this alveolus (O_2 15, CO_2 5, N_2 80). After obstruction of

the bronchiolus an equilibrium of gases inside and outside of the alveolus will be established. We shall consider the three gases separately.

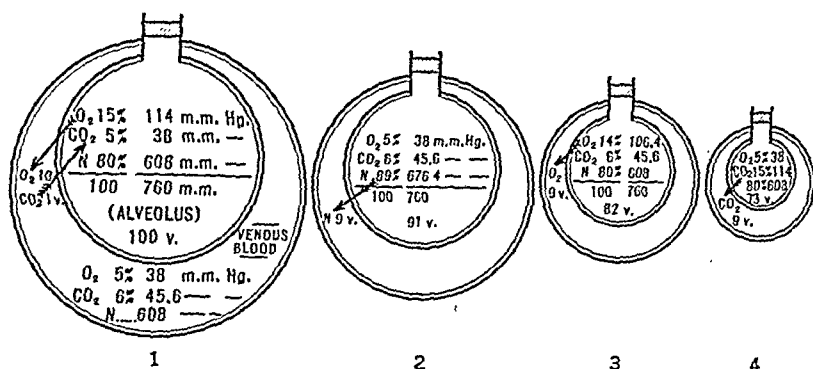


FIG. 2.—A schematic representation of alveolar gas exchanges, gradual gas absorption and shrinkage of the alveoli after complete bronchial obstruction. The absolute volume of the alveolus is only approximately indicated, but the figures are relative and demonstrate perfectly well the principles involved. In 1, 10 volumes of oxygen diffuse into the venous blood and 1 volume of carbon dioxide diffuses out of the venous into the alveolus. In 2, the alveolus has now lost 9 volumes of gas as stated under 1 and oxygen and carbon dioxide have come into equilibrium in the venous capillary blood and in the alveolus. However, the percentage and partial pressure of nitrogen have now been increased so that 9 volumes of nitrogen diffuse out of the alveolus into the venous blood. In 3, 9 volumes of nitrogen having previously diffused out of the alveolus into the venous blood, the percentage and partial pressure of oxygen or carbon dioxide have been relatively increased. For purposes of explanation let us say the oxygen has thus been relatively increased in percentage and partial pressure. Nine volumes of oxygen are now ready to diffuse out of the alveoli into the venous blood. In 4, 9 volumes of oxygen having diffused from the alveolus into the blood, we can consider that the carbon dioxide in the alveolus is relatively increased by these 9 volumes. Thus the partial pressure of this gas is relatively increased and carbon dioxide is ready to diffuse out of the alveolus. Thus the cycle continues until all the gases of the lung are absorbed, although actually the gas exchanges are going on simultaneously and not in the isolated way which we have ideally considered.

Oxygen represents 15 per cent of the gas mixture, and it is under a partial pressure of 114 mm. of mercury in the alveolus, whereas in the venous blood it is present to the extent of 5 per cent of one atmosphere and a partial pressure of only 38 mm. of mercury. (Fig. 2.) Therefore, 10 volumes of oxygen will pass from the alveolus into the blood; at the same time, and for similar reasons, 1 volume of carbon dioxide will pass in the opposite direction from the blood to the alveolus. In this way the gas mixture of the alveolus will lose 9 per cent of its original volume, so that instead of 100 volumes there is now 91 volumes. Now if the alveolar wall were a rigid structure the total pressure of gas in the alveolus would decrease and instead of a pressure of $114 + 38 + 608 = 760$ mm. of mercury, it would become $38 + 45.6 + 608 = 671.6$ mm. of mercury. Since the alveolar wall is a perfectly elastic structure, it is obvious that the alveolus will retract because the pressure around it is 760 mm.

of mercury. In fact the other lung being in connection with the atmospheric air, the intrapulmonary pressure in it is 760 mm. of mercury (the negative intrapleural pressure of from -4 to -7 mm. of mercury is comparatively so small that it is of little importance in this mechanism).

We shall now consider nitrogen. At the start, before bronchial occlusion, it represented 80/100 of the alveolar gas mixture. Now after the reduction in volume of the gas mixture it represents 80/91 of the gas mixture and its partial pressure has risen from 608 to 676.4 mm. of mercury. But this pressure is much higher than the pressure of nitrogen in the capillary blood; the excess of nitrogen will, therefore, pass into the blood. In other words, 9 volumes of nitrogen will be carried from the alveolus by the circulating blood, so that the volume of the alveolar air will be $91 - 9 = 82$ volumes.* (Fig. 2.)

This decrease in alveolar nitrogen disturbs again the equilibrium of oxygen and carbon dioxid between the alveolar air and the venous blood. Let us suppose that oxygen alone is affected by this imbalance. It is obvious that instead of 5 per cent, as it was previously, it will now represent 14 per cent of the alveolar gas mixture (N_2 80 + CO_2 6 + O_2 14 per cent) and, therefore, its partial pressure will rise to 106 mm. of mercury; so that now again 9 volumes of oxygen are ready to be carried away from the alveolus by the circulating blood. When this happens the volume of the alveolus will decrease to $82 - 9 = 73$ volumes.

The carbon dioxid will be affected in the same way (Fig. 2), and for similar reasons its percentage will rise from 6 to 15 per cent, corresponding to a partial pressure of 114 mm. of mercury, so that again 9 volumes of carbon dioxid are ready to be carried away by the circulating blood, thus reducing the volume from 71 to 62. The cycle is repeated, and 9 volumes of nitrogen will be ready to pass from the alveolus into the venous blood. Continuing this series of events, there will be a constant oscillation in gas values, and all the alveolar gases will be absorbed. In the open chest experiments we have noted that the initial absorption of gas is slow; after a while the lung seems to shrink much more rapidly; that is, there is an accelerated diminution in the size of the lung. Toward the end of the process when the great mass of gas has already been absorbed the process of absorption seems to slow down markedly, so that one may observe small isolated or patchy areas remaining practically unchanged over a long period of time. This mechanism is explained in Fig. 4, p. 332. The alveolus is represented by a

* These figures are not, strictly speaking, exact; for example, the volume of nitrogen in Fig. 2 = $80/91 = 87.9/100$ and the partial pressure corresponding to it equals 667.04 mm. of mercury. We prefer to give the figures as they are, however, because they simplify the explanation without altering any essential relations between the gases.

sphere, the radius of which is 1. The ratio of surface to volume is 3 to 1. Now suppose gases are absorbed so that the alveolus shrinks and its radius is one-half; the ratio of surface to volume is now 6 to 1. In other words, the volume of contained gases has been diminished much more than the surface of the alveolus, and there is relatively twice as much surface for the contained volume of gas as there was previously. This means that there is more absorbing surface for a unit volume of gas, and the alveolus will absorb a greater fraction of its contained volume of gas per unit of time than in the previous case. Thus, with the progressive shrinkage of the lung there is an acceleration in the absorption rate. However, this effect is offset by the impoverishment of the capillary circulation when the alveoli are markedly collapsed, so that in this way we can explain what we have actually observed: a slowing up of absorption toward the end of the process.

It is understood, of course that gas absorption does not occur in the schematic way we have here depicted; actually, there is an incessant simultaneous exchange of all the gases involved. Bohr has shown that extremely small differences in partial pressures are sufficient to insure the diffusion of great amounts of gases through semipermeable membranes. Loewy and Luntz have shown that a difference of only a couple of millimeters of mercury suffices for the passage through the alveolar membrane of the 250 cc. of oxygen per hour per kilogram necessary basically for a man at rest.

We have seen that the anesthetic vapors and oxygen are rapidly absorbed.* It is now easy to understand how atelectasis might develop during the course of an operation as in the cases reported by H. Santee and Bergamini and Shepard. Should complete bronchial obstruction by viscid bronchial secretions occur during the course of an operation and the lung area involved contain a high percentage of anesthetic vapors and oxygen, atelectasis could readily be produced within an extremely short time.

A word should be said further about the rôle played by nitrogen in the gaseous exchanges in the lung. We have seen that it is one of the inert gases, requiring many hours for its absorption. Oxygen and carbon dioxid alone are absorbed by the lung in a few minutes; but when oxygen and carbon dioxid are considered in the atmospheric mixture their absorption periods are greatly prolonged the nitrogen of the air acting as a physical brake by virtue of its slow absorption into the blood. For this reason should bronchial obstruction occur, the time required for the production of atelectasis would be measured in hours rather than minutes. In this way the nitrogen of the air may be considered as a fortunate circumstance of Nature to delay alveolar gas absorption and production of atelectasis. This delay is valuable because it allows an interval

* The reader should refer to the two previous articles of this series.

of time during which reaëration of the lung could still be easily accomplished. Thus nitrogen may be thought of as the "safety brake," especially during anesthesia and the postoperative period, and may be considered as the "mechanical buffer" of the air.

From the foregoing paragraphs it is seen that in the absorption of anesthetic gases and vapors the nitrogen of the air allows their dilution and acts as a "brake," delaying their absorption. Without this gas general anesthesia by inhalation would not be possible.

Comment. There are three possible objections to our theory:

1. An equilibrium between the gases of the blood and alveolar blood could be reached after bronchial occlusion, and this should stop further exchange of gases.

2. Much more carbon dioxid should pass from the blood into the alveoli, because its speed of passage through the alveolar membrane is 30 times as great as for oxygen; thus atelectasis would be impossible.

3. The negative intrapleural pressure on the affected side in atelectasis has often been reported so increased that it was surmised that it should cause a passage of gases from the blood into the alveolus, and in this way prevent atelectasis.

The first objection can easily be answered. If all the gas molecules contained in the obstructed alveolus are absorbed this is due to the perfect elasticity of the alveolar membrane and to the great difference in diffusion speeds through it of oxygen, carbon dioxid and nitrogen. For these reasons a perfect equilibrium is never reached, and as Loewy and von Schroetter first showed, the exchange of gases is represented by an asymptotic curve.

The second objection is based on the great speed of passage of carbon dioxid through the alveolar membrane as compared with oxygen or nitrogen. We have already mentioned the experiment with the frog's lung demonstrating this point. Exner, using a soap film, showed that carbon dioxid would pass through it toward an indifferent gas with a speed of about 10 cc. per minute per square centimeter when under a pressure of only $\frac{1}{2000}$ of an atmosphere. But the rate of diffusion of gases is regulated by their partial pressures, so that, although carbon dioxid passes rapidly from the blood into the alveolus after bronchial obstruction an equilibrium is reached when its percentage becomes about 6 per cent of one atmosphere in the alveolus; after this point the actual mass of carbon dioxid exchanged through the respiratory membrane is small. In other words, the exchanges of carbon dioxid are rapidly accomplished, but the actual amount of carbon dioxid passing through the respiratory membrane is regulated exclusively by the differences in partial pressure of the gases respectively in the alveolar and venous air.

The third objection is of even greater importance. Habliston, in 1928, found the intrapleural pressure on the atelectatic side in

4 cases in man to be -12 , -13 , -16 and -25 mm. of mercury respectively, as against -4 , to -7 mm. on the unaffected side. Farris reported 2 similar cases in which relief was obtained by artificial pneumothorax. Wilson and Gordon (quoted by Hablison) and Ashbury have also reported such cases. Ashbury reported a case with a negative intrapleural pressure of -16 to -20 mm. of mercury; after inducing a partial pneumothorax on the affected side with 600 cc. of air the pressure became -4 to -7 mm. of mercury.

Presumably, with a negative intrapleural pressure of -16 to -20 mm. of mercury the intrapulmonary pressure is also -16 to -20 mm. of mercury below atmospheric pressure, for the gases in the lung are under a pressure which tends to be equal to the intrapleural pressure. In the case of a lung which is completely obstructed the pressure of gases within it tends to equal the intrapleural pressure because of the elasticity of the alveoli; thus, if the intrapleural pressure were -20 mm. of mercury the intrapulmonary pressure would also be about 20 mm. of mercury less than atmospheric, *i. e.*, about 740 mm. of mercury. If we consider the percentages of oxygen and carbon dioxide in the entrapped alveolar air as 5 and 6 per cent, of one atmosphere respectively, their partial pressures would be 38 and 45.6 mm. of mercury when the intrapulmonary pressure is 760 mm. of mercury and 37 and 44.4 mm. of mercury with an intrapulmonary pressure of 740 mm. Therefore, in the case under consideration the effect of a -20 mm. negative intrapleural pressure would be to lower the partial pressure of oxygen and carbon dioxide in the alveolus by only from 1 to 2 mm. However, it must also be remembered that the gases in the alveolar capillary blood are also subjected to corresponding diminution in their pressures, so that from a relative standpoint the partial pressures of the gases in the alveoli and in the alveolar capillaries have not changed. We may thus deduce that the increased negative intrapleural pressure does not materially influence the exchange of gases in the obstructed lung.

So far as the therapeutic effect of artificial pneumothorax is concerned, we agree with the foregoing authors quoted, as to its palliative effect by decreasing the displacement of the heart, but we completely disagree as to its efficacy in freeing the air passages of obstructing material. Pneumothorax cannot further compress a lung already atelectatic. Lastly, collapse of the lung by pneumothorax does not favor re-aeration or penetration of air into this lung; on the contrary, deeper respiration by producing dilatation of the bronchi is more apt to lead to the formation of airways between obstructing mucus and bronchial wall with subsequent expulsion of the obstacle to respiration.

Increased pressure of the entrapped air as produced in coughing or strained respiration would theoretically accelerate the absorp-

tion of the alveolar gases, as has been maintained by van Allen and Adams. We think, however, that these authors have greatly exaggerated the importance of the factor, for an increase in intrapulmonary pressure in the obstructed lung can in these cases be produced only by an increase in the intrapulmonary pressure of the healthy lung. This means an increase in total intrathoracic pressure and consequently in the blood and blood gases as well. It seems that in these cases of van Allen and Adams, if atelectasis was produced earlier in animals incompletely anesthetized and struggling, this was due rather to excessive muscular work and exhaustion of oxygen in the blood, while at the same time rapid breathing washed out the carbon dioxid of the blood; the percentages of both gases and their partial pressures in the blood were decreased, causing a more rapid absorption of the entrapped air. We do not think, however, that from their data these authors were justified in coming to the conclusion that "narcotics are advisable because they aid in preventing atelectasis." The chief means the lung possesses to prevent atelectasis, or to overcome it once the bronchus is obstructed, is expulsion of the bronchial exudate by cough and deep breathing. Narcotics, on the contrary, deprive the lung of its best means of defense. We believe that for reasons previously described the more efficient treatment (both preventive and curative), besides rolling of the patient from side to side and encouraging him to breathe deeply, is hyperventilation by repeated inhalation of 10 per cent carbon dioxid in oxygen, (according to the method introduced by Henderson and Haggard in resuscitation after carbon monoxid poisoning), or bronchoscopic aspiration of bronchial exudate.

For a number of years we have endeavored to show that atelectasis is a well-defined clinical syndrome with a definite etiology, pathogenesis, pathology and treatment. It presents various clinical forms which can briefly be distinguished as follows:

1. According to the etiology: obstructive or compressive, post-operative or medical.
2. According to its distribution: multilobar (massive), lobar or lobular (patchy).
3. According to its duration: acute or chronic.
4. According to its evolution: simple or complicated.

The last variety comprises the cases in which infection follows because of the presence of the obstructing agent of microbes of more or less high virulence, so that an infectious process begins in the lung and is favored by the impaired drainage of the respiratory organ. Postoperative atelectasis in which Group 4 pneumococcus is always present represents a mild form of infection. Lobar pneumonia in which more virulent pneumococci are present represents another type of acute infectious atelectasis occurring as an accident in the course of pneumococcic bronchitis. Abscess and gangrene

of the lung are similarly infectious forms of septic bronchial obstruction and atelectasis, due to specific microorganisms, aërobes and anaërobes. The painstaking work of Smith, Allen, Joannides and others throws a new light on this last variety, justifying our conception.

We have also endeavored to prove that the pathologic process in the different forms of atelectasis develops along the same lines as in similar lesions in glandular organs, the ducts of which have been obstructed and to which the lung should be compared. We have shown that the circulation and the ventilation in lungs that have become atelectatic, from any cause, show exactly parallel changes, depending entirely on the condition of the pulmonary ventilation.

The present work, by showing the intimate mechanism of the production of apneumatosiis, can explain the pathogenesis of the different forms of the disease by sound physiologic principles. It shows, further, the importance of physiologic, physical and chemical consideration in the study of respiration in relation to thoracic surgery. Clinical and experimental evidence points to the conclusion that atelectasis is always due to complete bronchial obstruction. We wish to stress the great importance in the pathology of the lung of impairment of free bronchial drainage, and we believe that it has been demonstrated beyond doubt that atelectasis must be definitely associated with the idea of bronchial obstruction. The obstructing agent, whatever its nature, should be sought and treatment instituted for its removal and reaëration of the lung.

General Conclusions. 1. Experimental methods have been devised which give evidence that when a bronchus is completely obstructed the entrapped alveolar air rapidly undergoes qualitative and quantitative changes as determined by successive gas analyses.

2. Qualitatively, the percentages and partial pressures of the gases comprising the alveolar air tend to, but never quite, reach an equilibrium with the gases of the venous blood.

3. Quantitatively, the entrapped alveolar gases pass through the respiratory membrane into the blood circulating in the perialveolar capillaries until complete airlessness of the involved area is produced.

4. The mechanism of production of atelectasis in the compressed lung (pneumothorax, pleural exudate, intrathoracic tumors, etc.) is exactly the same as in bronchial obstruction.

5. Besides the gases of the air, diffusion of other gases was studied by introducing them into a lung previously rendered atelectatic. The different gases used in these experiments were: (a) Active gases, oxygen and carbon dioxid; (b) neutral gases, hydrogen, nitrogen and helium; (c) anesthetic gases or vapors, ether, ethyl chlorid, nitrous oxid and ethylene.

6. A new experimental method was devised which allows direct vision of the pulmonary changes occurring during the experiment.

7. Nitrogen in the respiratory air plays the part of a "mechanical buffer," retarding the absorption of more diffusible and more soluble gases.

8. This experimental work has allowed the formation of a theory on the mechanism of atelectasis based on the physiology of exchange of gases in the lung.

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THE PATHOLOGY OF RHEUMATIC PNEUMONIA.

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THE pulmonary manifestations of rheumatic fever have been studied by many clinicians. Many years ago Fuller,¹ Cheadle,² Garrod³ and other English physicians wrote of "Rheumatic Pneumonias." It is probable that these earlier writers recognized clinically lesions similar to those which are the subject of this report. Some of their observations correspond very closely to what is today being identified as the clinical picture of rheumatic pneumonitis and rheumatic pleurisy. Garrod mentioned the transient character of the physical signs of the pulmonary lesions, but he stated that there is nothing peculiar in the postmortem appearance of such a lung or its pleura which would differentiate it from the ordinary acute inflammations.

Pulmonary lesions in the course of rheumatic fever are certainly not infrequent, as evidenced by the reports of Fuller,¹ Latham,⁴ Cheadle,² Garrod³ and in recent years by Thayer,⁵ Swift,⁶ Rabinowitz⁷ and Paul.⁸ They have been recognized rather commonly in the more severe cases of rheumatic fever studied by Dr. J. C. Small and ourselves at the Philadelphia General and Presbyterian Hospitals.

Until very recently, knowledge of the incidence and character of these changes has been based mostly on clinical observations. Pathologic study was inconclusive.

Among the lesions which others have described are: (1) Rheumatic fibrinous pleurisy; (2) rheumatic pleurisy with effusion; (3) atelectasis secondary to pleural effusion; (4) atelectasis secondary to

enlarged heart or pericardial effusion; (5) vascular lesions, involving the pulmonary aorta and its branches.

The above list does not include the pulmonary changes commonly caused by cardiac decompensation, such as hydrothorax, passive congestion and infarction of the lung, both static and embolic.

Rheumatic pleurisy, meaning a specific inflammatory lesion, similar to rheumatic pericarditis and polyarthrits, was among the earliest recognized features of rheumatic fever. Despite the fact that it was accepted as a rheumatic manifestation, little attempt was made to establish its status by pathologic description. Longstreth,⁹ of the Pennsylvania Hospital, described the marked fibrinous character of this pleurisy and pointed out the rarity of empyema as a complication. Bezançon and Weill¹⁰ studied the chemical composition of the pleural effusion with especial reference to its fibrin content. They, as well as others, recorded a predominance of endothelial cells in rheumatic pleurisy. In 1928, Paul⁸ made an excellent review of the history of the pleural and pulmonary lesions and described the specific nature of the pleurisy.

The vascular lesions are the specific changes that have been observed in the pulmonary artery, its branches, and especially the arterioles. They are identical with the vascular lesions seen in the aorta and in many of the viscera and are characteristic of rheumatic fever. Other acute infections are known to produce focal necrotic lesions in the aorta and the arterial branches, but rheumatic fever is now recognized as the most important cause of this type of lesion. Discovery of this vascular damage has been a recent contribution to the rapidly-increasing knowledge of the nature of rheumatic fever.¹¹ Acute rheumatic involvement of the pulmonary aorta and its larger branches has been of little or no clinical significance.

Pleurisy is a common manifestation of the serous membrane involvement in the active stages of the disease. Undoubtedly it has been the cause of many, or in certain cases most, of the physical signs that led to the diagnosis of "rheumatic pneumonia," and to the unusually high incidence of that complication in the statistics of Latham and Fuller. It is seen in the majority of those cases that have come to necropsy in the acute or subacute phases of rheumatic fever. It may be present in most extensive degree, accompanying a widespread mediastinitis and pericarditis, productive of the classical signs and symptoms of acute pleurisy, and is then usually followed by effusion. It also may exist in small isolated patches of fibrinous exudate, usually over the lower lobes and to a lesser degree on the upper lobes. These smaller patches, as with similar lesions on the epicardial surface are seldom detected by physical examination. We are entirely in accord with Paul's findings as to the frequent incidence of rheumatic pleurisy, and as it is not the subject of this report the reader is referred to his article for its detailed description.

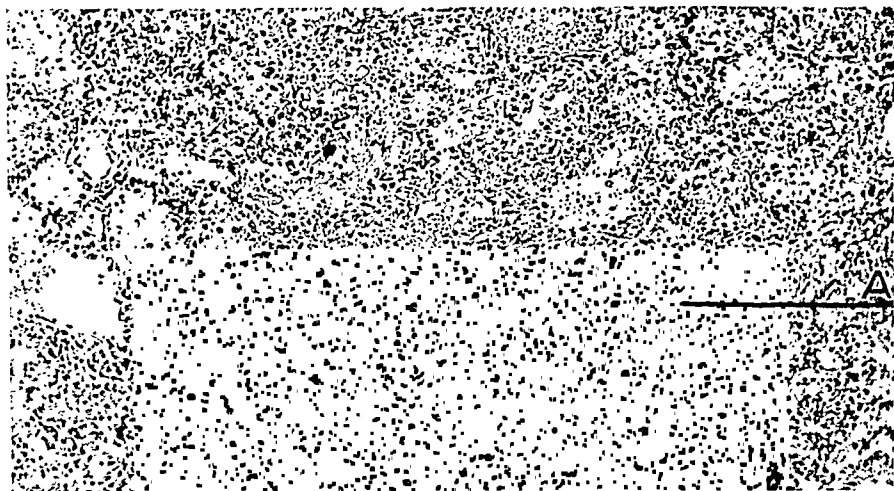


FIG. 1

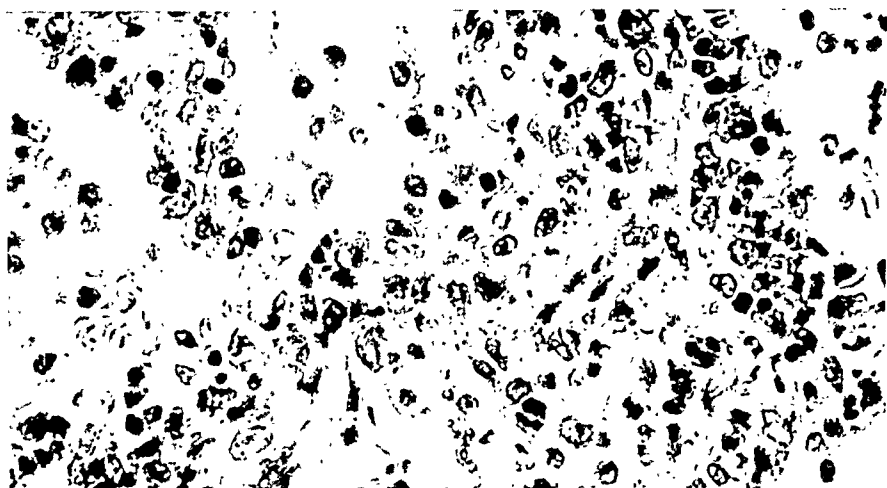


FIG. 2

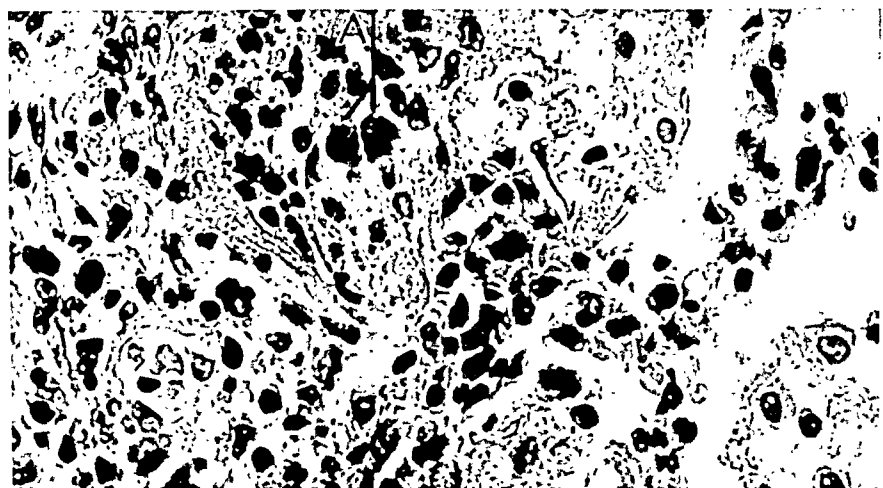


FIG. 3

FIG. 1.—(Case 1.) Low power; rheumatic pneumonia. The alveoli are filled with blood and fibrin; the walls are thickened with inflammatory exudate (A).

FIG. 2.—(Case 1.) High power, showing interstitial infiltration, consisting mostly of endothelial cells and fibrin. Many cells are pyknotic. The cellular content of the alveoli is scanty. ($\times 552$)

FIG. 3.—(Case 1.) Dense infiltration, with obliteration of the alveoli. Note large basophilic cells, and Aschoff cells with two or three nuclei (A).

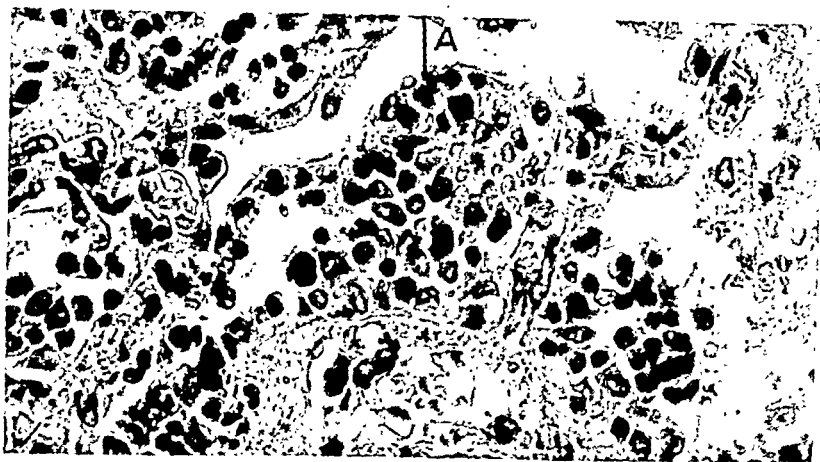


FIG. 4

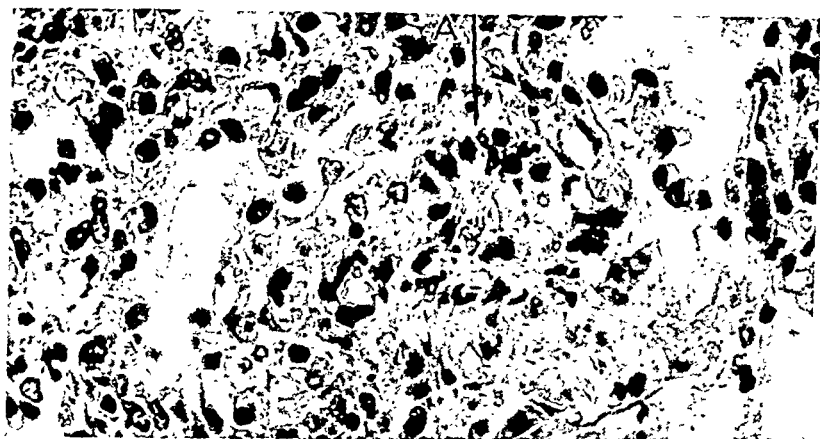


FIG. 5

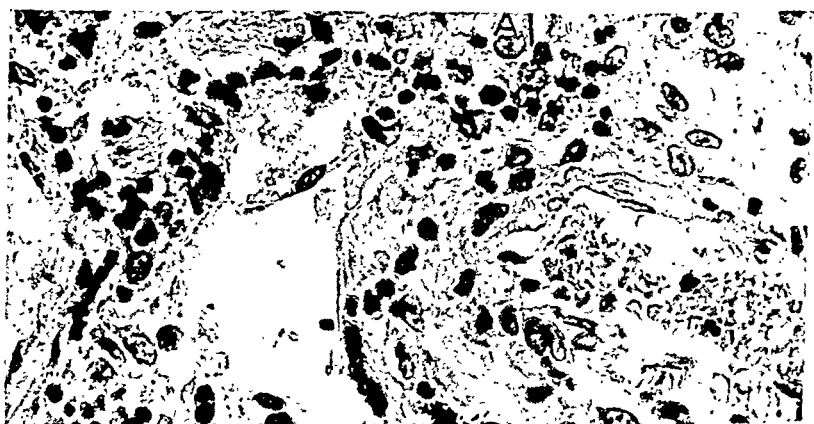


FIG. 6

FIG. 4.—(Case 1.) Perivascular nodule of large basophilic cells (proliferative lesion). Note bulging of the lesion into the alveolus. ($\times 552$.)

FIG. 5.—(Case 1.) Showing early necrotic interstitial focus. Note irregular concentric arrangement of epithelioid cells (A).

FIG. 6.—(Case 1.) An arteriole showing invasion of the adventitia and media by a submiliary nodule (A). It does not reach the intima. ($\times 552$.)

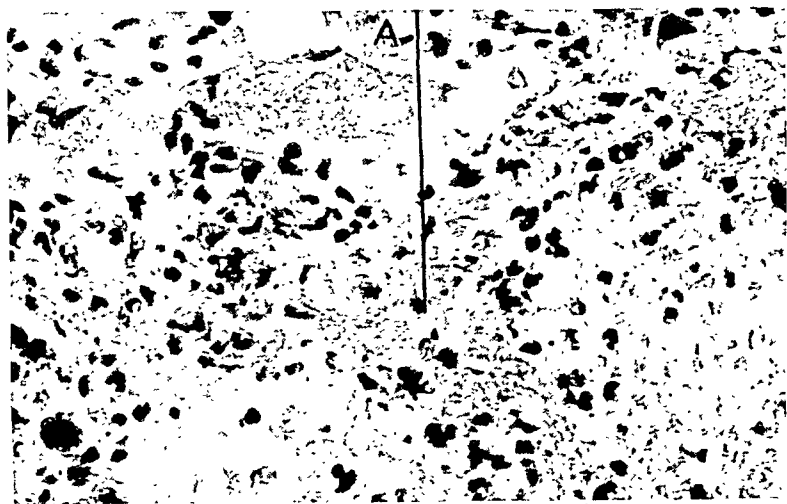


FIG. 7

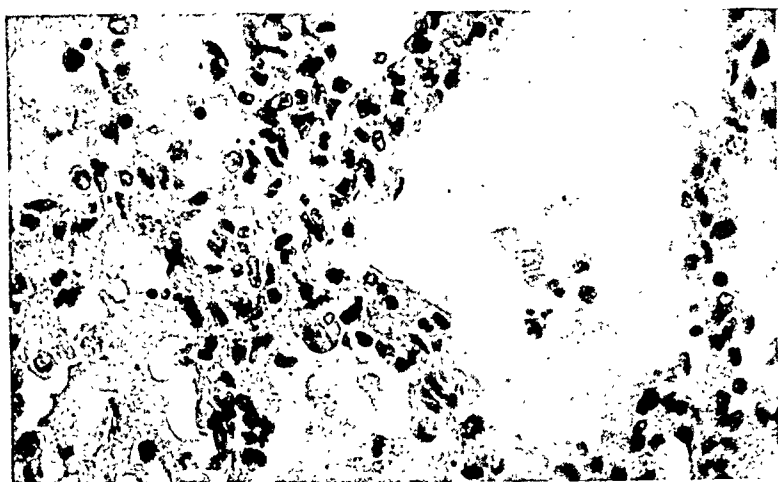


FIG. 8



FIG. 9

FIG. 7.—(Case 3.) Rheumatic interstitial pneumonia. The alveolar walls are necrotic and are converted into broad irregular bands of fibrin (A). The infiltrating cells are the irregular epithelioid types. One giant cell is seen in the lower left corner. The alveoli contain erythrocytes.

FIG. 8.—(Case 5.) Acute infiltration of irregular epithelioid cells and fibrin in the alveolar walls. Fibrin and serum fill the alveoli.

FIG. 9.—(Case 5.) Rheumatic nodule in wall of pulmonary artery (A). Hyalinized and vascularized adventitia (B).

FIG. 10

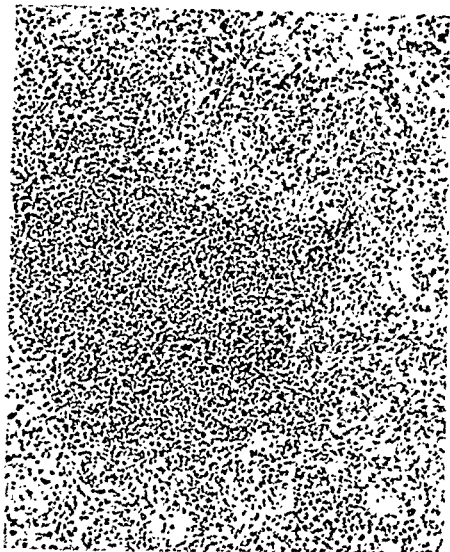


FIG. 11

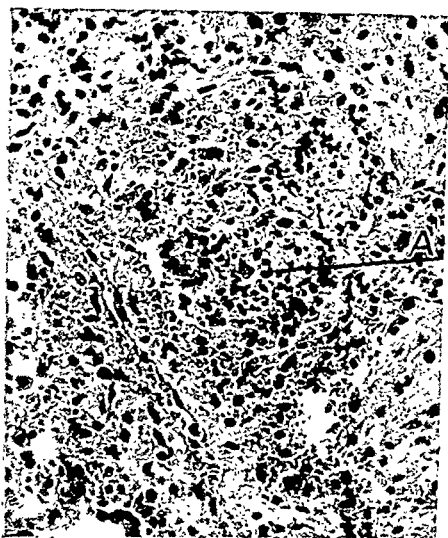
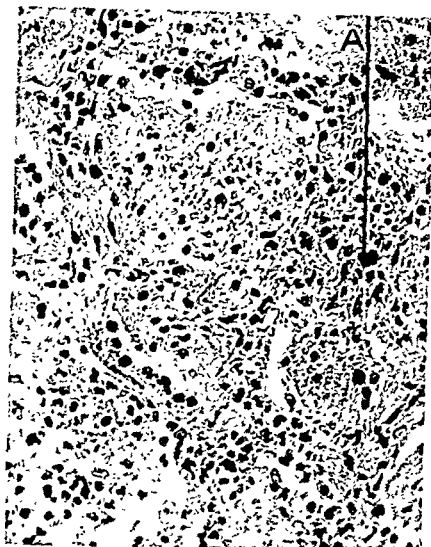


FIG. 12

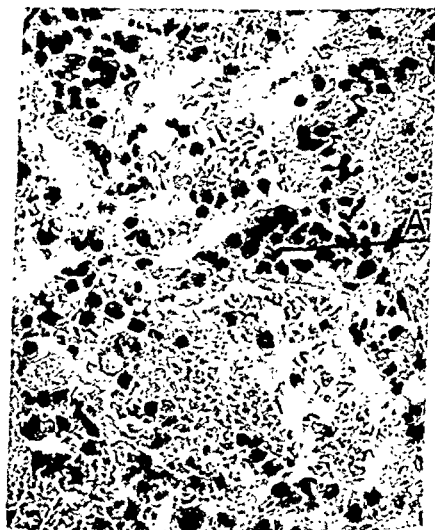


FIG. 13

FIG. 10.—(Case 6.) Unusually large nodule in rheumatic pneumonia, consisting of endothelial, epithelioid and polymorphonuclear cells. The adjacent lung tissue is completely consolidated.

FIG. 11.—(Case 6.) Rheumatic pneumonia showing Aschoff nodule (A), with many of the alveolar walls converted into strips of fibrin. The alveoli are filled with fibrin and blood and some contain a few polymorphonuclears and endothelial cells.

FIG. 12.—(Case 6.) Aschoff nodule in rheumatic pneumonia.

FIG. 13.—(Case 6.) Typical Aschoff nodule in the alveolar wall (A). The adjacent interstitial tissue is invaded by epithelioid cells. The alveoli are filled with red blood cells and fibrin.

Patients with rheumatic fever, particularly if severe, may frequently exhibit a clinical picture suggestive of lobar pneumonia. This pulmonary involvement may appear about the same time as do the acute cardiac disturbances; it is usually preceded by the appearance of arthritis, but certainly not in every case. The symptoms common to acute rheumatic fever are, of course, seen with this pneumonitis. It does not depend apparently upon the presence of an upper respiratory infection, differing thus from the usual bronchopneumonia; it does not present the striking features of the classical picture of lobar pneumonia—chill, prolonged and high fever, rusty sputum, severe pleural pain and marked elevation of the respiratory rate. On the contrary, its symptoms are usually not spectacular; initial chill, heralding the pulmonary invasion, does not occur; cough may, or may not, be troublesome; it is productive of a scanty tenacious sputum, presenting no special bacteriologic findings; occasionally it may be blood streaked. The fever is irregular; it is often high (102° to 105° F.), reflecting the severity of the general infection. There is a moderate elevation of the respiratory rate.

The physical signs assume a greater prominence than do the symptoms. Dullness to percussion and bronchial breathing are frequent and characteristic findings. They may be found at the bases in either lung, laterally in the axillary areas, or even in the upper lobes. One entire lobe may appear to be involved; two or more areas may be consolidated at the same time. A striking feature in many cases is the transient character of the several consolidations, analogous to the course of the polyarthritis. In some cases the signs of consolidation may be prolonged as much as a week or more. It usually lasts from 2 to 4 days. Consolidation may recur in the same area within a few weeks in unusually virulent infections. The signs of consolidation are often followed by dullness with absence of breath sounds due either to pulmonary collapse or pleural effusion. Such signs may persist for many days or weeks. Râles may or may not be present in the stage of consolidation. They are of variable quality and seldom, if ever, are heard in the same number and intensity as in lobar pneumonia. In the later stages, large and coarse friction râles are frequently heard and can be ascribed to a plastic pleuritis.

The signs of consolidation, according to the best authorities, represent atelectasis rather than an actual pneumonitis. The statistics of Latham, made over 80 years ago, are in disrepute, being based mostly on unsupported clinical observation. That the striking pulmonary signs heard in these acutely ill patients are not caused solely by pleurisy has been the conviction of a number of observers. Bezançon and Weill¹⁰ and Goyena¹³ employed the term "cortico-pleuritis" to indicate that a subpleural zone of congestion or inflammation existed together with the pleurisy. The lesion was

described as "splenization" by Besnier,¹⁴ *i. e.*, not a real exudative lesion, but rather an intense hyperemia and edema with collapse and atelectasis of lung tissue. Coombs,¹⁵ the English authority on the pathology of rheumatic fever, considered atelectasis and passive congestion as the chief lesions in the production of these signs. However, he mentions the possibility of consolidation appearing in the right upper lobe, an area relatively immune from the complicating influence of cardiac failure.

If a pneumonia does exist, is it a specific lesion? Garrod did not think so.³ Occasionally lobar pneumonia, due to the pneumococcus, complicates acute rheumatic fever, and other infections have been encountered. Thayer,⁵ reporting a series of 25 fatal cases of rheumatic fever, noted terminal pneumonia or bronchopneumonia in 50 per cent of the cases. Paul⁸ noted that in more than half of 30 cases, there were evidences of a focal hemorrhagic lesion, rather widespread, involving individual lobules or groups of lobules, which might be interpreted as an early or hemorrhagic state of broncho- or lobular pneumonia. Certain atypical features were present, *i. e.*, the extremely hemorrhagic character of the intra-alveolar exudate and a difficulty in isolating the commoner types of bacteria usually associated with bronchopneumonia. Although it seems to have been a fairly characteristic finding in his cases, he did not think that the evidence warranted its description as a specific lesion. He came to the conclusion that such a lesion limited to individual lobules was insufficient to give rise to appreciable areas of dullness to percussion and that the widespread physical signs were caused by other processes, notably pulmonary atelectasis and pleural effusion.

Rabinowitz,⁷ in a recent discussion, concluded that a specific pneumopathy did occur, clinically distinguishable from lobar pneumonia and from bronchopneumonia and that the ultimate proof of its existence would be made with the discovery of Aschoff lesions in the consolidated lung.

The chief stumbling block in according this rheumatic pneumopathy a specific status has been the absence of a precise pathologic description, which in turn depends on the fact that few cases of rheumatic fever die in the course of an acute attack, especially in the initial attack, where pulmonary changes are not clouded by the evidence of chronic cardiac failure that has been produced by successive attacks of the disease.

A study starting in 1927 of the pulmonary lesions in a small series of fatal cases of acute rheumatic fever has convinced us that the clinical picture of consolidation depended upon the presence of a specific pneumonia or pneumonitis. It was specific in that the lesions were essentially those characteristic of rheumatic fever elsewhere in the body and had developed in patients who had rheumatic fever with acute cardiac involvement. A preliminary report of

this lesion, hitherto undescribed as far as we know, was made at a meeting of the Philadelphia Pathological Society in December, 1927.¹⁶ Naish,¹⁷ a short time afterward, described pulmonary lesions in rheumatic fever that are strikingly similar to those we then presented.

This report is based upon the study of 9 fatal cases of acute rheumatic fever that presented pulmonary lesions. Six of the patients were from the Philadelphia General Hospital, 1 from the Presbyterian Hospital, another from the University Hospital, through the kindness of Dr. Baldwin Lucké, and the ninth case from the Jewish Hospital.

Case Reports. CASE 1.—A. N., a boy, aged 11 years, was admitted to the Philadelphia General Hospital on June 11, 1927, and died June 21, 1927. For 2 weeks he had painful swelling of various joints. On admission the arthritis had largely subsided, but he was apathetic and toxic. The temperature ranged between 100° and 103° F.; the pulse rate was 120 to 140 and the respiratory rate was 26 to 30; the leukocyte count was 19,000. Cardiac examination revealed a double murmur at the apex. There had been a previous attack of rheumatic fever 2 years before. On June 14 there was noted a pericardial friction rub and a suggestion of choreiform twitching. On June 15 there was dullness and bronchial breathing over the left base, posteriorly. June 16 there was noted, in addition, dullness over the right base. On June 18 the choreiform movements became marked. The pulmonary signs were practically the same. The patient became very toxic, constantly twitching and suggesting cerebral involvement. He died on June 21.

Gross Morbid Anatomy. There was an acute pancarditis: mitral and aortic valvulitis, rheumatic myocarditis and fibrinous pericarditis. The outer surface of the pericardium, especially on its right aspect, was covered with a very thin fibrinopurulent exudate which also covered the adjacent mediastinal pleuræ. Cultures from the pleural and pericardial exudates, the heart blood and lung tissue were sterile over several weeks. About 300 cc. of fairly clear serous fluid were removed from the right pleural sac and about 100 cc. from the left.

Lungs. The mucosa of the trachea and large bronchi was moderately congested. The peribronchial and mediastinal lymph nodes were enlarged, soft and edematous. Both lungs showed the same unusual changes. They were moderately enlarged, bulky and did not collapse. They presented a rich variation in color: the lower lobes were solid and deep blue, which contrasted with the yellow or the grayish-white of the more aerated tissue. Smaller reddish-pink and brownish patches were scattered over the entire pleural surface. On section the tissue was dark reddish-brown in color. The surface of most of the cut section of the lower lobe was firm, non-crepitant and unusually smooth as compared to the granular surface presented in lobar pneumonia. The surface was fairly dry in its most airless portions, but somewhat edematous toward the outer part of the lobe. Blocks of tissue from these heavier portions of the lower lobes sank in water. This infiltration differed from an ordinary lobar or lobular pneumonia by the fineness or absence of the granularity, by a smooth liver-like consistency almost resembling atelectasis, but without any gross evidence of collapse, the lungs remaining bulky. On detailed inspection a very fine grayish lattice work, outlining lobules, was noted.

Pathologic Histology. A number of sections taken for histologic study show an acute inflammation of the lung tissue, which manifests itself as

an interstitial cellular infiltration and an alveolar exudate. The interstitial involvement is the more significant of the two (Figs. 1 and 2).

The alveolar walls are thickened because of capillary congestion, edema and cellular exudate. These lesions are not uniform in their distribution. The interstitial tissue sometimes appears slightly prominent because of capillary congestion; in other places it is markedly thickened by cellular infiltration, coalescing in many places into dense aggregations. In such areas the alveolar walls have disappeared and the normal lung architecture is obliterated (Fig. 3). Fibrin, in a liberal amount, appears within the infiltrates. These cellular collections, which are often of nodular or semi-nodular appearance, seem to start in perivascular locations, gradually radiating out into the interstitial spaces. Practically all are in intimate relationship with bloodvessels, large or small (Fig. 4). The edematous and fibrinous quality of this perivascular infiltration is striking.

The cellular complexion of these lesions is not constant. Most prominent are large, deeply stained cells, with vesicular nuclei, often multinuclear and markedly basophilic (Figs. 3 and 4), sometimes comprising the larger part of the exudate. One also notes a varying number of plasma cells, lymphocytes and an occasional polymorphonuclear. Fibrin and detritus help complete the picture. The large cell with vesicular nucleus, described here stained with methyl pyronin stain (Pappenheim stain), shows a reddish cytoplasm. These cells are known in the submiliary nodules of rheumatic fever as the Aschoff cell; their origin from the lining endothelium of small bloodvessels is accepted by many and they will be referred to in this report as endothelioid cells.

In other fields one notes a fairly large cell, not quite the size of the large Aschoff cell and with an irregularly shaped nucleus that is very deeply stained. The cytoplasm shows a basophilic reaction. The shape of the nucleus may be roughly oval or comma shaped, or sometimes triangular or arrow shaped. These cells are seen side by side with the larger cells and in some areas almost to the exclusion of the latter.

There is also seen a more slender and elongated and much more irregular cell, almost all nucleus, identical in appearance with the epithelioid cell of a tubercle. They very probably have an endothelial origin in common with the other cells described, but their difference in appearance and manner of deposition should be emphasized. In this report they shall be referred to as epithelioid cells. They are seen best in the small focal lesions, apparently very early foci, in which the giant cells are not present. There is a central necrosis composed of fibrin, swollen and broken up connective-tissue fibers, into which these epithelioid cells infiltrate. Together with the larger solidly nucleated cells they frequently present a concentric arrangement around the center of the lesion, or their grouping may present ring-shaped or rosette-shaped figures (Fig. 5). There is a superficial resemblance of these lesions to a tubercle, but there is one essential difference—the tubercle is avascular.

The alveoli are filled with serum and blood where the inflammatory process is most acute. The alveolar contents vary directly in amount with the degree and acuity of the interstitial involvement. In general the cellular constituent of this alveolar exudate is scanty. The lining epithelium is desquamated and often no other cells are seen within the air sacs.

Cellular prolongations of the interstitial infiltration are seen pushing their way into the alveoli, and so these large cells and accompanying lymphocytes can be seen free in some broken-down alveolar spaces.

Very occasionally one notes a few sacs packed with polymorphonuclears. However, this whole pathologic picture is characterized by their absence or, at best, their scantiness. They are present in modest numbers in the small foci of necrosis.

The bronchial branches show no evidence of mucosal inflammation but most of the bronchioles do show a peribronchial cellular infiltration of the type described above, with increased vascularity and edema. This infiltration may surround the whole tube or invade it locally in seminodular appearance.

Sections of the pleura show no exudate or very little. Sections from the mediastinal pleura have not been included. In most places the endothelial surface is intact. The subpleural tissue, however, is thickened from cellular infiltration, invading and obliterating the subpleural alveoli.

The bloodvessels throughout the lung are congested. Perivascular edema, even around the capillaries, is marked. Although many of the vessels are packed with erythrocytes, no definite thrombi are noted. The smaller vessels, arterioles and venules show a marked endothelial hyperplasia. The capillaries and lymphatics occasionally show this as well. The perivascular infiltration at times appears contiguous with the cells of the capillary endothelium, giving the impression that these large cells are of endothelial origin. In the walls of the larger vessels there are occasional infiltrations extending into the adventitia and media (Fig. 6). They do not appear in these sections to invade the intima nor to reach the endothelial surface in the large bloodvessels. Weigert stains do not show any definite destruction of the elastic fiber in these larger vessels, but damage is found in many smaller vessels.

Summary. The histologic study of these lungs showed an acute interstitial inflammatory process, characterized by hyperemia, edema, and a perivascular infiltration of large endothelioid cells, multinuclear giant cells, plasmocytes, lymphocytes and relatively few polymorphonuclear leukocytes. The staining and general appearance of the endothelioid and giant cells are identical with those found in the Aschoff lesions occurring in the myocardium of the same patient.

CASE 2.—F. R., male, aged 19 years, was admitted to the Philadelphia General Hospital on June 6, 1927, to the service of Dr. J. C. Small; he died June 28, 1927. At the age of 13 years he had an attack of rheumatic fever which confined him to bed for 8 months. The chief complaints on entering the hospital were joint pains, dyspnea and profuse sweats. The heart was enlarged and its action irregular. There were double aortic and mitral murmurs and a Corrigan pulse. On June 14 distant breathing sounds and moist râles were heard over the right lung, anteriorly and laterally in the third interspace. On June 15 a pleural friction rub at the right base was noted. The râles had disappeared within 2 days but the breath sounds remained distant and were accompanied by coarse friction sounds. The cardiac disease and pleurisy were the outstanding clinical manifestations. Death occurred from heart failure.

Gross Morbid Anatomy. Both pleural sacs were partially obliterated by numerous, rather easily broken fibrous adhesions, which provided sacculations, especially at the bases, and were filled with slightly turbid fluid, about 50 cc. from each side being recovered and cultured with negative results. In some sacculations the fluid was almost gelatinous.

The lungs, heart, trachea and esophagus were removed *en masse*. The peribronchial and mediastinal lymph nodes were soft and edematous but not much enlarged. The pericardial sac was completely obliterated by fibrous adhesions. There was marked acute exopericarditis manifested by violaceous hyperemic patches, without purulent change, extending to and

involving the right mediastinal pleura. The heart was greatly enlarged and showed aortic and mitral valvulitis and sclerotic infiltration of the ventricular membranous septum.

The left lung weighed 380 gm. It was of the normal grayish-pink color and air-containing throughout, except at the base where collapse had occurred. The pleural surface was covered with edematous fibrous adhesions. The lower lobe, posteriorly, showed an acute fibrinous pleurisy. There were many hyperemic areas with the pleural surface gray and translucent, through which very small subpleural nodules could be seen. There were no areas of definite consolidation. On section the lung tissue was grayish-red and crepitant, except for the atelectatic zone at the base. No pus could be squeezed out of the bronchioles.

The right lung weighed 350 gm. It was similar to its fellow, showing the same type of pleural pathology, areas of localized hyperemia, an absence of bronchial inflammation and consolidation, but showing also some basal atelectasis.

Pathologic Histology. The pleura is thickened by a cellular infiltration that is accompanied in some areas by edema and in other areas by a hyaline fibrosis. The infiltration consists mainly of large mononuclear cells, with vesicular basophilic nuclei and cytoplasm. They are diffusely and densely distributed, the only suggestion of localization being around small blood-vessels, whose walls are lined by the same type of cell seen throughout the tissue. Lymphocytes occur in smaller numbers. Polymorphonuclears are present, but only in the fibrinous exudate on the pleural surface. Giant cells appear occasionally.

This endothelioid infiltration extends down into the underlying lung tissue, gradually fading out, giving a distinct thickening of the interstitial walls, blending into the atrophy of emphysema. A few irregular epithelioid cells are also present. Some of the subpleural fibrous tissue is very much swollen, resembling acutely hyalinized fibers. They are swollen, broken up and infiltrated by these large endothelioid cells. The alveoli contain no exudate and only slight desquamation of epithelial cells appears.

The large bloodvessels do not present any abnormalities. They are congested, but do not show any thrombus formation. The smaller vessels exhibit thickened walls and, especially in the areas where the cellular changes are most marked, an extraordinary degree of hyperplasia of the endothelium. Occasionally "Herzfehler" cells are seen in the tissues and a few in the alveoli.

Summary. Acute and subacute pleurisy; subacute and chronic interstitial subpleural pneumonitis; basal atelectasis.

CASE 3.—E. H., a white girl, aged 15 years, entered the Philadelphia General Hospital on the service of Dr. McLean on June 2, 1928. She had been treated in a tuberculous clinic for 3 months because of fever and blood-streaked sputum. On admission the patient was found to be extremely weak, thus preventing a thorough physical examination. She had marked anemia, a leukocytosis, an enlarged heart with signs of mitral valvular disease, a mild icterus and an enlarged, tender liver. There was a history of chorea and growing pains 3 years ago. In the lung examination the resident physician found posteriorly, in both lower lobes, dullness on percussion, distant breath sounds and a few fine crackling râles. Death occurred on June 5, 1928. Diagnosis: myocardial degeneration and anemia.

Gross Morbid Anatomy. Heart: hypertrophy and dilatation and rheumatic pancarditis. There was an acute verrucal endocarditis of the aortic valve, a mitral stenosis, characteristic left auricular pathology and a fatty degeneration of the myocardium. Pericarditis was not present.

The left lung weighed 530 gm., the right lung 520 gm. Both lungs showed the same unusual changes. They did not collapse but remained bulky. The lower lobes contained large consolidations, occupying their larger part and extending up toward the hilum. These areas were of a dark-blue color and quite sharply outlined against the surrounding aerated tissue. The lower part of the upper lobes contained similar firm and dark blue infiltrations along the interlobar fissure, but the apical portions were pale and emphysematous in marked contrast and were spotted and splotched by small, bluish-red foci of hemorrhage. The pleura showed no changes except a slight dullness over the consolidations. In these locations there was noted a thickening of the lymphatics and interlobular partitions, which formed a prominent grayish-white network. The lower lobes, on section, showed well-demarcated areas which were solid, brownish-red in color, with a finely granular surface and without any points of suppuration. The immediate basal areas of both lungs were comparatively normal. The bronchi showed a moderate congestion with a swollen mucosa, but no exudate; the peribronchial lymph nodes were moderately edematous and the larger bloodvessels had no gross lesions.

Pathologic Histology. The striking features are the prominent interstitial infiltration of cells and the accumulation in the alveoli of large amounts of fibrin and many "Herzfehler" cells. The pleura is normal. The interstitial thickening of the walls is quite diffuse, but in many places the cellular infiltration is heavy enough to assume nodular or seminodular shapes. The background for the hyperplasia often appears to be a collection of fibrin and necrotic material around tiny apertures of bloodvessels.

The predominating cells are medium sized, long or oval-shaped mononuclear cells. They may be designated as epithelioid cells and have little or no cytoplasm. Many of the nuclei are hyperchromatic and take very irregular shapes, *e. g.*, arrow-, club- or comma-shaped. The irregularity of these nuclei is a striking feature. Their presence is associated with necrosis. The alveolar walls are converted into broad irregular strips of fibrin (Fig 7). Weigert stain shows a complete loss of elastic fibers in these swollen alveolar walls. In many places there are large numbers of these epithelioid cells deposited indiscriminately, and again in other places they present a concentric arrangement around small bloodvessels, the lumina of which are partially obliterated. A number of broken-down polymorphonuclears are seen in these infiltrations, especially where necrosis appears. Some large multinucleated giant cells are seen in the large seminodular collections and a few lymphocytes are noted.

The larger vessels show a marked endothelial hyperplasia. Many of the small vessels are partially obliterated by this process.

Other sections emphasize the intense interstitial infiltration collapsing the alveoli, except where they contain some exudate. This is not primarily an atelectasis, in that where the alveoli are maintained by the presence of their contents, their thick walls are shown to excellent advantage. The alveoli contain "Herzfehler" cells, fibrin and the remains of red blood cells. The bronchi are normal.

Summary. This lesion is an inflammatory process in the lung tissue and not passive pulmonary congestion. This will be taken up in the discussion.

CASE 4.—M. M., a colored girl, aged 16 years, entered the Presbyterian Hospital March 21, 1927, on the service of Dr. Pemberton. Two years before she had had an attack of acute rheumatic fever with joint pains, precordial pain and hemoptysis. Tonsillectomy was performed in May,

1926, followed by intermittent joint pains. Three weeks before admission she developed an acute polyarthrititis, a heavy cough and blood spitting. Temperature on admission was 105° F.; the leukocyte count was 17,300. Physical examination showed an acute pharyngitis and signs of bronchopneumonia, scattered areas of dullness and râles in both lungs, posteriorly. The heart was enlarged and a presystolic murmur was heard at the apex. Death occurred on March 28, 1927, due to heart failure. The clinical diagnosis was rheumatic fever and acidosis.

Gross Morbid Anatomy. The heart was markedly dilated. There was an increased amount of pericardial fluid, hemorrhagic and containing fibrin. There was a verrucous valvulitis of the aortic, mitral and tricuspid valves and a fatty degeneration of the myocardium. The left pleural sac contained about 30 cc. and the right pleura 100 cc. of fluid, clear and amber-colored. The pleural surfaces were smooth and glistening. The left lung weighed 650 gm. There was no crepitation, posteriorly, over the lower two-thirds. The color of the lung was mottled, pale pinkish, with irregularly-scattered areas of slate blue, the largest blue area being posteriorly in the lower lobe, measuring 9.5 by 8 cm. These areas contained no air, they were rather leathery in consistency and the cut surface was smooth, glistening and brownish-red in color. In contrast there was an area in the upper lobe, yellowish, granular and solid, presenting the aspect of ordinary lobar pneumonia. There were, in this case, 2 distinct types of consolidation. The right lung weighed 660 gm. It exhibited the same lesions as its fellow, except that the involvement by both the slate-blue and the pneumococcic consolidations were not as extensive.

Pathologic Histology. Section I (from the blue areas of infiltration). The lung tissue is filled with edema. The interalveolar tissues are thickened by a cellular exudate, consisting of irregularly-shaped cells, with solid nuclei, together with broken-down polymorphonuclears and fibrin. There is an occasional very large basophilic mononuclear cell and a couple of giant cells are noted. The infiltration is thin but widely diffused. There are many small perivascular collections of cells. There is some peribronchial infiltration by these cells; the other bronchi appear altogether normal. The histology here is not as spectacular as in Cases 1 and 3, but is characteristic. The cellular infiltration is nonsuppurative but consists of cells, the exact copy of which are present in undoubted rheumatic lesions of the myocardium in the same patient.

A section from the yellowish-red, granular consolidation of the upper lobe shows, in contrast, the heavy uniform alveolar exudate of polymorphonuclears and fibrin that characterizes the gray hepatization of lobar pneumonia. The alveolar walls are thin and the capillaries are compressed. There is comparatively no interstitial exudate.

Summary. Acute interstitial rheumatic pneumonitis and pneumococcus pneumonia, involving different lobes of the same lung.

CASE 5.—C. Y., a Siamese student, aged 19 years, was admitted to the University Hospital on the service of Dr. Stengel on February 26, 1928. He had an attack of acute rheumatic fever in August, 1927, confining him to bed for 2 weeks. Mitral stenosis subsequently developed. A tonsillectomy was performed in December, 1927. In February, 1928, he had another attack of joint pains, dyspnea, cough and fever. On admission, physical examination revealed an enlarged heart, mitral stenosis and passive congestion of the lungs. The leukocyte count was 19,000. He ran an irregular fever for 2 weeks; had a short remission and then had a prolonged fever; pericardial friction was present from time to time. There was a

progressive downward course and he died on May 9 from cardiac failure. Clinically, the lung signs were interpreted as being due to passive congestion. The necropsy was performed by Dr. Baldwin Lucké.

Gross Morbid Anatomy. Heart: acute pericarditis; recent rheumatic endocarditis of the mitral, aortic and tricuspid valves. Lungs: lobular pneumonia. The gross description by Dr. Lucké is as follows: The left lung weighs 500 gm.; the right, 800 gm. Both organs were of average size and had a very colorful appearance. The basal lobes and areas of the upper lobes are bluish; the others have a pink, still others a dull-red appearance. The basal lobes, particularly in their posterior portions, feel firm. The rest of the tissue had a boggy consistency. Here and there the pleural surfaces, particularly over the basal lobes, were somewhat dull, but there was scarcely any fibrin visible. The cut surface of the basal lobes showed large patches of grayish-brown, bluish and dull red, finely and coarsely granular consolidation, between which lies heavily congested and edematous lung tissue. The consolidations are mostly along the posterior wall and the bronchi have normal caliber. Their mucosa in places was deeply reddened and swollen. Frank pus was nowhere present.

Pathologic Histology. The pleural tissue was prominently thickened, not by superimposed exudate, but by edema, congestion, hemorrhages and a cellular exudate in the subpleural tissue. One notes large, irregularly-shaped cells, occasionally multinucleated. They may streak diffusely through the fibrous tissue, but their perivascular distribution is striking. The subpleural bloodvessels are tremendously dilated and some of them are the seats of hemorrhage. They show a marked hyperplasia of the endothelial lining. The endothelial layer of cells that constitutes the pleural surface is mostly intact. It is broken up in some places and there has been an eruption of fibrin and cells out on the surface.

The lung tissue presents a number of striking features. Although the alveolar walls are slightly thickened throughout by a mild increase in cellularity and edema, their undue prominence is caused by focal perivascular infiltrations, consisting of the large, deeply-stained cells described previously, accompanied by fibrin and endothelial hyperplasia of bloodvessels. These large cells have a basophilic cytoplasm and are often multinuclear. Such larger collections, with the exudative features predominating over the destructive or necrotic, are characteristic of the Aschoff type.

Again one notes the slender, very irregular epithelioid cells often massed in small collections and their long axes radiating from some central point or approaching rosette formation, or again totally irregular in their disposition (Fig. 8). The alveoli are almost universally filled with serum, fibrin and blood.

There are large areas of infarcted tissue, the appearance of which, however, is very different from that of ordinary infarction. While the tissue is flooded with blood and the alveolar lining cells are destroyed, the interstitial tissue is tremendously thickened by fibrin and cellular exudate. These new cells have retained some degree of viability. Many of the nuclei are broken up, but they possess enough staining to indicate that they are the same type of cell seen in the noninfarcted areas. Together with fibrin this exudate has caused tremendous thickening of the alveolar walls in contrast to the skeletal framework left behind in ordinary lung infarction. In and around the infarction, one notes numerous early focal necrotic lesions.

A large bronchial tube is filled with blood; the mucosa is intact. There is no evidence of suppurative inflammation but the capillaries of the submucosa are dilated and there is a rich infiltration throughout the bronchial wall of the perivascular, seminodular, endothelioid exudate seen throughout the lung.

Many of the bloodvessels, large and small, show a tremendous thickening of their walls. (Note: This patient was only 19 years old.) In many, the adventitia and periadventitial tissue are thickened by hyalin fibrosis. Some of them exhibit acute or subacute foci involving one or all three of the vascular layers (Fig. 9).

Some of the larger branches of the pulmonary artery are partially, and others entirely, occluded by what, on superficial examination, might pass for ordinary organization of thrombus; but there is no thrombus, no trace of blood pigment to be seen, and the new intravascular tissue is distinctly inflammatory in type, rather than mere organization. One notes a rather loose edematous collection of fibroblastic tissue, containing many small capillaries, congested and hemorrhagic, surrounded by cellular exudate, large irregular cells, epithelioid cells and lymphocytes.

Summary. This case presented an acute inflammatory process in both lungs—interstitial, perivascular and practically nonsuppurative, with typical Aschoff cells and not associated with inflammatory changes of the bronchial mucosa. On gross inspection, what appeared to be an example of this unusual consolidation, was found to be complicated by infarction. Obliterating rheumatic arteritis contributed to the formation of this infarction.

CASE 6.—W. M. S., a colored girl, aged 17 years, entered the Philadelphia General Hospital on July 9, 1928, with an acute polyarthritis. She gave a vague history of previous attacks of rheumatic fever; salicylate therapy was instituted, but her condition became worse. There was always marked tachycardia, although the joint symptoms subsided temporarily. On August 15 the patient was transferred to the service of Dr. J. C. Small, with a diagnosis of mitral endocarditis, pericarditis and recurring arthritis. Serum therapy was started. The temperature ranged from 98° to 103° F, and the pulse rate was 100 to 170. The white blood cell count was 19,000. The course was progressively downward. On August 22 an impaired percussion note was noted, with diminished breath sounds and some dry râles from the fourth interspace to the base of the right lung. The respiratory rate was 28; the pulse 130 and the temperature 101° F. By August 31 all the signs of rheumatic pneumonitis had vanished. On September 17 and 18, and at later times, there were attacks of auricular paroxysmal tachycardia. On October 2 râles were noted in both lungs, but especially in the right middle lobe and associated with tubular breathing. On October 10 there were signs of consolidation in the lower left lobe. On October 11 bronchial breathing and egophony were heard in both lower lobes, posteriorly. The intensity of the signs in the right lung lessened within two days. Again on October 29 there were signs of consolidation over the lower halves of both lungs. Parotitis and nephritis developed and the patient died on November 4. The clinical diagnoses were rheumatic pancarditis, with hepatic congestion, nephritis and bronchopneumonia.

Gross Morbid Anatomy. The autopsy (Dr. E. Weiss) revealed a subacute and chronic adhesive pericarditis. The valve structures were apparently normal.

The description of the lungs is as follows: "The right lung weighs 460 gm. The upper lobe is voluminous and pinkish-red in color. The lower lobe is smaller, firm and almost entirely solidified. On section it is dark red in color, with areas that are granular in appearance and resembling bronchopneumonia of some duration." We examined these lungs through the kindness of Dr. Weiss and found that the lower lobes were solid, dark red

in color, and in many areas showed a very thin fibrinous dulling of the pleural surface. On section there was noted a consolidation with a finely-granular surface, dark red in color and of rubbery consistency. There were also small, grayish-red, firm areas and granular, apparently bronchopneumonic, although no fluid pus was noted. There was no suppuration in the bronchial tree.

Pathologic Histology. The pleura is moderately thickened by a fibrosis; the subpleural capillaries are congested. The pulmonary lesion is not uniform. In some fields the alveoli are partially aerated and contain small or moderate numbers of erythrocytes. Their intra-alveolar walls are thickened by congestion and small isolated groups of endothelial cells. Epithelioid cells and smaller round cells are noted. The striking features are large foci scattered throughout the section, superficially resembling abscess formations (Fig. 10), nodular and some so large as to nearly occupy the entire low-power microscopic field. Others are much smaller, occupying an area the size of one or two alveolar spaces. They do not have regular contour. In some places a tendency to demarcation is present, but it soon is lost in a gradual extension into the surrounding lung tissue by infiltration along thickened alveolar walls and by gradually thinning out in various directions. Other areas show lung tissue consolidated by tremendous outpouring of red blood cells and fibrin into the alveoli. The cellular exudate within the alveoli is scanty except where the interstitial infiltration has heaped up and "poured" out into the alveoli, through broken-down walls. Marked fibrinous thickening and degeneration of alveolar walls is notable. In some places this fibrinous infiltration is so marked and homogeneous, accompanied by occlusion or obscuration of the capillary, that the alveolar walls have the appearance of strips of ribbon (Fig. 11).

The interstitial cellular infiltration is the same as noted in previous cases, except that the nodule formation assumes unusual prominence, equivalent to or greater than that seen in the great majority of acutely rheumatic hearts. These focal lesions are of various sizes, ranging from the very small but definite Aschoff collections (Figs. 11, 12 and 13) to the very large lesion that occupies the larger part of microscopic fields. The large nodules consist of densely-packed endothelioid cells, polymorphonuclears, round cells and detritus. Many cells apparently have broken up and the original lung tissue has been replaced by a background of fibrin. The picture is very suggestive of an acute granulomatous lesion. It was seen grossly as a small grayish-red nodule and was then interpreted as being an indurated or "chronic" bronchopneumonia. In one field a bronchial branch is seen partially filled with this cellular exudate, which is an extension of a large adjacent nodule. This appears to be an infiltration of a bronchiolar wall with local destruction. The remaining portion of the wall presents a normal appearance. The smaller nodules are typical rheumatic lesions, containing the various cellular elements that have been described. The giant cells with two to three nuclei are seen in most of the nodules. Polymorphonuclears, while numerous in the large granulomatous lesions, are relatively few in the smaller collections and the diffuse interstitial exudate. The bloodvessels show the same adventitial and medial infiltrations as seen in the previous cases.

Summary. Acute interstitial rheumatic pneumonia.

CASE 7.—R. S., a white girl, aged 17 years, was admitted to the Philadelphia General Hospital on the medical service of Dr. A. A. Stevens, with soreness over the entire body. The patient was a normal child until 3 years ago, when, at the age of 13 years, she had an acute illness characterized by fever, chills, sore throat, excessive sweats and pain in all joints of the body.

She was confined to bed for several weeks. When she recovered from this acute attack she was left in a very nervous state and frequently had twitching of various parts of the body. The diagnosis was St. Vitus' dance.

Six weeks ago, while coming from Scotland, she began to feel badly and to have slight sore throat; twitching continued intermittently. Three weeks ago she was again forced to bed with chills and fever and a severe sore throat. She again noticed pain and stiffness in her neck, followed in a few days by pain in both knees, both ankles and right shoulder. She has been very short of breath since the onset 3 weeks ago.

Physical examination showed the presence of a severely toxic infection. The heart was considerably enlarged; a presystolic rumble, a harsh mitral murmur and irregular rhythm were noted. The latter varied between a flutter and a fibrillation of the auricles. A mild icterus was present. The white blood cell count was 13,900. The blood culture was sterile. Diarrhea became a troublesome symptom. Progressive cardiac enlargement was noted, followed by hepatic and splenic enlargement. Two days before death the patient complained of great pain over the precordium and in the right chest. Apparently no physical signs were elicited; the critical condition of the patient prevented a more adequate examination.

Gross Morbid Anatomy. Autopsy (Dr. G. Robson): Gross anatomical diagnoses were: obliterative pericarditis; chronic mitral and aortic endocarditis (rheumatic); pneumonia (rheumatic type) of the right lung. Dr. Robson's gross description of the lungs is as follows: "The left lung weighs 365 gm. The pleural surfaces were normal. The lung is crepitant throughout and on section the surface is not excessively bloody. A few small reddish areas of solid consistency are present in the lower lobe. The right lung weighs 590 gm. A large portion of the lower and a small part of the upper lobe were consolidated. On section these portions of the lung have a reddish, fleshy appearance and were nonair-containing. The appearance, while resembling atelectasis, does not seem to involve collapse of the lung and suggests some type of acute pneumonitis."

Pathologic Histology. A section from the right lower lobe shows a consolidation of the lung tissue. The pleura is not included. Most of the consolidation is caused by the filling of the alveoli with serum, fibrin and hemorrhage. Many of the alveoli contain no cellular infiltration or very few cells, there being an occasional phagocyte and desquamated epithelial cell. In many areas the alveolar hemorrhage is marked. In contrast to the slight cellular infiltration in the alveoli, one notes an undue cellularity in the alveolar walls, variable in intensity. It is moderate throughout most of the section, consisting of small collections of very irregular, usually oval or comma-shaped, medium-sized and deeply-staining cells, often in and around a necrotic area with a background of fibrin. Many of these small groups of cells are collected around congested capillaries. There are in addition large areas densely cellular, so that in lower magnifications the original lung architecture is made out with difficulty. One of these larger infiltrations is perivascular, spreading from a large branch of the pulmonary artery, out into the surrounding lung tissue in an interstitial manner, but the alveolar walls are so thickened by the new cells and by edema that the alveolar spaces are often compressed or collapsed.

The type of cell has been described: irregular, elongated, deeply staining, with little or no cytoplasm and accompanied by small, round cells and occasional polymorphonuclears. A few large hyperchromatic cells are present, but the multinuclear giant cells are not seen.

The bronchi show no definite change. The larger bloodvessels show a surrounding zone of edema, invaded by numbers of the new cells. A few alveoli, three or four, are densely packed with polymorphonuclears.

Summary. Interstitial rheumatic pneumonia.

CASE 8.—B. D., a white woman, aged 48 years, was admitted to the medical service of the Philadelphia General Hospital on July 5, 1928 with the complaint of pain and swelling in the ankles and wrists. The onset occurred 2 weeks before with pain in the metatarsal joints. On June 28 the ankles were involved, and on July 4 the left wrist and fingers were swollen and painful. Fever and anorexia accompanied the arthropathy. The past medical history consisted of measles in childhood, anemia from the age of 15 to 20 years and influenza in 1918; since that time there have been repeated attacks of tonsillitis. Dyspnea, palpitation and occasional edema of the ankles have been noted as transient attacks for the past few years. There has been no previous history of rheumatic fever and no history of precordial or chest pain. One sister had many attacks of rheumatic fever. Three children died in early years of infection, apparently unrelated to rheumatic fever.

Physical examination on July 5 showed a painful swelling of many of the larger joints, particularly the wrists and ankles, making movement impossible. She had a fever of 101° F. and a pulse rate of 100. The tonsils were enlarged and infected. Marked venous pulsation was seen in the neck. Lung examination was negative. The heart was enlarged, especially to the left; the rhythm was regular and a rough systolic murmur was heard at the base. Treatment was followed by no definite improvement. On July 13 a cardiac irregularity developed. July 18 the patient was transferred to Dr. Small's rheumatic fever service. A consolidation, as indicated by bronchial breathing and dullness, was found in the base of the right lung. Serum therapy was tried, but without avail. Fibrillation, cyanosis and abdominal distention developed and the patient died on July 23. Laboratory data: Red blood cells, 3,700,000; with blood cells, 17,000; hemoglobin, 3.2 gm. A throat culture was positive for streptococcus cardioarthritidis. Blood culture was negative; blood urea nitrogen, 16.

Gross Morbid Anatomy (Dr. Konzelman). The heart weighed 790 gm. and presented a typical rheumatic pancarditis. The aortic valve was stiffened by previous disease and a recent verrucous endocarditis. The left lung weighed 390 gm. and the right, 650 gm. The lesions were much the same in both lungs but more pronounced in the right. The upper lobes were grayish mottled by black carbon deposit. The apical portions and the anterior edge seemed overdilated and paler. The remaining part of each lung was a bluish-red and at the base appeared slightly depressed. The entire lower lobes were a deep blue. Subserous petechiae were scattered over the entire surface and a few dark pea-sized nodules were seen on the pleural surface. Section shows the upper lobes to be gray and crepitant while the lower lobes were dark red and airless. The bronchial mucosa was pale red and smooth. Diagnosis: interstitial pneumonia.

Pathologic Histology. There was an acute and subacute interstitial pneumonitis accompanied by marked capillary congestion. The cellular infiltration was similar to those described in the preceding cases, except that it was more uniform and without the presence of distinct nodular formation. There was no polymorphonuclear invasion. In many places the alveolar walls were markedly thickened. The diminution in alveolar space might be interpreted as a partial atelectasis, but the pneumonitis was the predominant change. In the same fields many of the alveoli were distended by hemorrhage or edema, but no exudate.

CASE 9.—R. I., a young white male, aged 26 years, was admitted January 13, 1931, to the Jewish Hospital on the medical service of Dr. E. I. Becker, with a diagnosis of lobar pneumonia and empyema. He died on January 16, 1931. One month before he felt chilly and then feverish. Soon afterward he had several drenching sweats and at the same time began to cough up a brownish sputum. With every cough there was a sharp pain

in the right side of the chest. This pain and expectoration gradually abated. For 2 weeks he had been moderately jaundiced. On January 12 he became extremely short of breath and his fever, which had been irregular and decreasing, reappeared. He was admitted to the hospital on the following day. He never had a sore throat and there was no joint inflammation in this attack.

At the age of 8 years he had an attack of rheumatic fever. Five years before admission he was treated in another hospital for cardiac disease. For many years he has been somewhat short of breath.

Physical examination revealed moderate jaundice. Respiration was rapid and shallow. Examination revealed a flat percussion note from the right base up to the fifth rib and an impairment from that level to the second interspace. The breath sounds over the right lower lobe were distant and tubular. The left side was resonant and a few coarse râles were heard over the entire chest. The heart was much enlarged, both to the left and right. Thrills were palpable over the aortic area and the whole right parasternal region, and to some extent at the apex. Blowing murmurs were heard at both the mitral and aortic areas.

The patient was obviously too ill for detailed examination. He was perspiring freely; cough was not frequent and it was unproductive. He had no chill since the first part of his illness 1 month ago. His temperature, which on admission was 101° F., fluctuated between 98° and 102° F.; the pulse rate was 110 to 160 and the respiratory rate was 28 to 40. On January 14 his condition appeared to be improved; marked impairment was limited to the right lower lobe and the temperature was normal. Roentgen ray examination on this date showed "a consolidation at the right root and base, with a probable plastic pleurisy along the lateral aspect of the chest. There is no distinct evidence of fluid in the pleural cavity and, if present, is very scant. The left lung is clear." On January 16 some elevation of fever was noted. The physical signs in the right lower lobe remained unaltered except for complete loss of breath sounds; râles, previously infrequent, were heard over the entire right lung and a few at the left base, where percussion was moderately impaired. Later, on that day, the patient became extremely dyspneic and cyanotic. Oxygen and stimulation did not help and death occurred rather quickly in a patient who on the previous day had shown considerable clinical improvement.

On January 13, 1931, hemoglobin was 74 per cent; red blood cells, 4,000,000; white blood cells, 18,000; neutrophils, 86 per cent; blood sugar, 0.125; blood urea, 20; blood culture was negative; sputum cultures, none (patient scarcely coughed).

Gross Morbid Anatomy. Acute mediastinitis, involving the mediastinal pleuræ and exopericardium, rheumatic pancarditis and widespread bilateral pneumonia were the salient features. The heart weighed 700 gm. and exhibited an acute fibrinous pericarditis over the base. The hypertrophy was due to stenosis of the aortic, mitral and tricuspid valves.

The spleen was enlarged, blackish-red and firm. It did not possess the pulp hyperplasia of ordinary pneumonia. The liver was partially destroyed by a severe passive congestion.

The left lung weighed 800 gm.; it was moderately enlarged. The upper lobe was aerated, gray in color, but spotted by foci of hemorrhage. The lower lobe was consolidated and dark red in color. Section showed this lobe to be entirely solidified, dark reddish-brown with occasional fine grayish markings suggestive of interstitial thickening. The granularity was very fine and in some areas was lost. The lobe was moderately larger than normal. There was no sign of suppuration. The bronchial tree was moderately congested but showed no distinct inflammatory reaction. The upper lobe was emphysematous and congested.

The right lung was consolidated in all three lobes. It weighed 1100 gm. and was moderately enlarged. It was dark reddish-blue and slate-colored. Over the lateral aspect of the lower lobe was a fibrinous hemorrhagic pleuritis. Section showed a complete solidification, dark reddish, with an almost smooth surface, fleshy and suggestive of the appearance of firm, deeply congested splenic tissue. Some areas were rusty-brown in color. Fine grayish markings were seen occasionally as in the other lung, and the bronchi presented the same negative findings. The lymph nodes were dark and moderately edematous. Examination of the pulmonary artery showed throughout both lungs an extreme degree of atheromatous degeneration. In the lower part of the right upper lobe there was a recent infarction. Section showed a laminated grayish occlusion of the arterial branch at the apex of the infarction. The appearance was suggestive of arteritis and thrombosis. All bacteriologic studies at necropsy were negative.

Pathologic Histology. The pleura in numerous sections show a slight thickening, due to a moderate subpleural edema. There is no acute inflammatory reaction, except over an infarction, where the endothelium has been disrupted and a thin layer of fibrin deposited.

The alveoli are filled with masses of red blood cells and fibrin. In some places there has been apparently a rupture of the alveolar wall followed by an overflow of blood. Practically every alveolus is involved. The lining epithelium is swollen and partially desquamated. Only an occasional white blood cell is seen in the alveolar contents. The notable exception to this is the presence of large numbers of pigment-laden phagocytes in some alveoli. In contrast to the character of the alveolar exudate the interstitial tissue (interalveolar walls) is remarkably thickened. This change is seen throughout all fields, varying only in degree. Capillary congestion and hemorrhage and endothelial hyperplasia are seen in the least affected areas. The more frequent changes are a focal and also in many fields, a diffuse cellular infiltration of epithelioid cells, round cells and an occasional polymorphonuclear. The number, dark staining and the irregular shape of the epithelioid cells are striking. Often they appear to be fragmented. Fibrin is present in large amounts; some of the alveolar walls are represented by broad strips of fibrin, in which are found numbers of epithelioid or fragmented cells. In such places a severe grade of necrosis is evident. Weigert stain shows marked destruction of elastic tissue. Small nodular foci are scattered throughout; in some fields they have broken through the alveolar wall, projecting in bulbous collections into the alveolar space. Occasionally large nodules of the same type are found which obliterate two or even many alveolar spaces. A few nodular thickenings contain the larger Aschoff cells, including small giant cells with two or even three nuclei.

Sections through the infarct of the right upper lobe show that the widespread interstitial and nodular infiltrations have not been entirely destroyed by the ischemia and are easily recognized at the periphery of the infarction. Large and small branches of the pulmonary artery are completely filled or their lumina reduced to small channels by an edematous granulation tissue. Other vessels show an acute arteritis and thrombus. One large branch in longitudinal section shows a large portion destroyed by an acute, dense cellular infiltration that extends through the entire wall and fills a part of the lumen. The structure of the original three vascular layers, including all of the elastic tissue has been destroyed. Another vessel, where the inflammatory process is less advanced, is dilated and its thin wall is diffusely invaded by epithelioid cells such as are seen in the lung parenchyma; a large sector of the media is destroyed and replaced by fibrin. The thrombus is invaded by epithelioid and round cells. Another large vessel, which was partially occluded by granulation tissue apparently the result of a previous

inflammation, is heavily infiltrated by the same acute cellular process that was found in the lung tissue, the mediastinum and heart of the patient. All normal structure in this vessel, except a fibrous adventitia, has been obliterated. It appears that an acute recurring arteritis of specific rheumatic type, is responsible for the infarction.

Outside of the infarcted area the smaller vessels all have some degree of thickening. The adventitia, particularly, shows an excess of hyaline fibrosis. Many contain small foci of acute inflammation and necrosis in the media. The arterioles show an endothelial hyperplasia, often to the point of occlusion. The profusion of interstitial fibrin and infiltration often obscures the capillary structure. In many places the latter has disappeared.

The bronchioles are often filled with blood and fibrin. Their walls may be thickened by congestion and edema. At some points there is noted a rupture of the wall with extrusion of the interstitial fibrinous exudate, often laden with phagocytes. In the larger branches the mucosa is intact and no intrabronchial pathology is evident.

Summary. Rheumatic lobar pneumonia, involving the entire right lung and left lower lobe. There was a history of pneumonia and pleuritis at the beginning of this patient's last illness one month before. The final lung changes apparently represent a recurring attack.

Discussion. The term "rheumatic pneumonia" present in old medical literature, has been practically forgotten in the last half century. The tendency to precision in medical thought and nomenclature caused "rheumatic pneumonia" to follow "typho-malaria" and other dubious terms into the discard. Until a few years ago "rheumatic fever" meant essentially acute arthritis and endocarditis. Today a widespread involvement of many tissues is recognized. The advance is due in most part to the recognition of a specific pathology, which began with Aschoff's description of submiliary nodules in the heart.¹⁸ At the present time identification of a rheumatic lesion depends on histology; the presence of focal perivascular lesions, necrotic and proliferative of the Aschoff type, is the criterion for diagnosis. Recently there has been considerable discussion as to specificity of the Aschoff lesions for rheumatic fever. While something similar is apparently produced in experimental animals by the injection of many strains of nonhemolytic and possibly hemolytic streptococci, it is seen in human pathology pre-eminently in rheumatic fever and we consider it characteristic in the cardiac lesions of that disease.

This series of cases was chosen from a large number of rheumatic fatalities, because it represents a small group of patients dying in the acute stage of the disease, who presented definite pulmonary signs, usually of consolidation. Many other patients having the same clinical picture, but surviving after a stormy course, have been seen in the last four years. Other cases, similar to those included in this report, have been observed at necropsy, but for various reasons could not be included in the pathologic study. A large number of rheumatic deaths presented the characteristic find-

ings of subacute and subchronic pleuritis with effusion and basal atelectasis. They do not fall within the scope of this report, apparently representing a later stage of rheumatic pulmonary disease and often complicated by cardiac failure. One such case included in this series (Case 2, F.R.) clinically presented pleurisy, cardiac failure and atelectasis, and at necropsy, isolated foci of pneumonitis without consolidation.

In our study the gross and histologic examinations revealed pulmonary changes which apparently had not been previously described. They were presented at the December meeting of the Pathological Society of Philadelphia, 1927, and published in an abstract in the *Archives of Pathology*, 1928.¹⁶ It was therefore, with great interest that we read the paper on the "Rheumatic Lung," by A. E. Naish¹⁷ whose findings are identical with our own.

The acute pulmonary lesion of rheumatic fever, rheumatic pneumonia or pneumonitis, is an acute interstitial inflammation, having as its basis the vascular damage and perivascular infiltrations that are common to all acute rheumatic lesions. It is practically non-suppurative, thus differing from the acute interstitial pneumonias caused by hemolytic streptococci, such as are associated with epidemic influenza¹⁹ or the bronchopneumonia of measles.²⁰ In none of our 9 cases was there any considerable exudate of polymorphonuclear cells. In the most acute stages, characterized especially by necrosis, one sees groups of polymorphonuclears, scanty in number and sharing in the karyorrhexis suffered by all cells in these areas of acute focal necrosis. The nonsuppurative character of this inflammation precludes the development of pyogenic changes, such as gray hepatization, abscess or empyema, except through the medium of secondary infection.

Consolidation was present in 8 of these cases and did not seem to show a preference for one lung over the other. Both lungs were involved and usually to about the same extent. In Case 4 (M.M.) the left lung showed a greater involvement than the right lung. In Case 9 (R.I.) 4 lobes were consolidated, including the entire right lung. The largest consolidations were in the lower lobes with smaller infiltrations in the upper lobes, especially toward the hilum and along the interlobar fissure. Although an entire lower lobe was often involved, consolidation was not as bulky as in lobar pneumonia. The rheumatic lesion's color, varying from dark blue to a rusty-brown, and the delicate white tracery under the pleura, due to interstitial exudate, and its appearance on section, are distinct features. The dark red, firm finely-granular, slightly moist cut surface, doubtless led to its description as a "splenization." Naish points out its resemblance to solid India rubber. It is not atelectasis. The physical signs elicited in the examination of the lungs of acutely ill rheumatic fever patients, have often been attributed to atelectasis. It was noted in only 1 of these 9 cases (Case 2, F.R.)

where there was no consolidation, but basal collapse associated with subacute and chronic pleuritis. Basal collapse, sometimes to an unusual degree, and often accompanied by gelatinous edematous pleural adhesions, is seen frequently in subacute aspects of the disease. Our belief is that the lesion described in this report is either independent of those changes or, in more probability, precedes them.

We would speak of this lesion as pneumonia or pneumonitis, depending upon its extent. Small hemorrhagic foci, with little or no cellular infiltration, often seen in the nonconsolidated lobes of these cases and indeed in many cases of rheumatic fever with virtually no pulmonary involvement, scarcely merit the title of pneumonia or of "hemorrhagic lobular pneumonia." However, if the presence of inflammatory consolidation with the subsequent alteration of physical signs warrants the use of the term "pneumonia," the lesions in 8 of the cases in this series can well be called "rheumatic pneumonia." As a fine distinction, in contrast to the ordinary bronchopneumonia, this consolidation could possibly be termed "perivascular pneumonia."

Histologic examination gives definite proof of the identity of the lesion. This brings up the point as to what is the characteristic microscopic picture of a rheumatic focus. Evidently, as stated in the protocol of the first case, the cellular complexion of these lesions differs in different locations. The difference seems to depend on the age of the lesion and to a lesser degree in consideration of the disease in general, on the organ that is involved. The areas of acute focal necrosis, small perivascular groups of broken-up polymorphonuclears and slender irregular epithelioid cells might conceivably be the first of a number of phases of inflammatory reaction and to be followed later by a more proliferative process, the Aschoff "nodule." This more mature stage of the reaction is characteristic and its presence establishes the diagnosis of rheumatic fever. It is this interstitial perivascular infiltration of large cells, often multinucleated, that is a significant part of the histologic picture in rheumatic pneumonitis.

A third phase of this reaction is suggested by the presence of fairly large cells, with solid irregular nuclei replacing the large Aschoff cells and giving the impression that such a lesion is a subacute one, verging on early sclerosis.

Another important feature is the vascular destruction that is usually seen in rheumatic pathology—the endothelial hyperplasia, the rupture of capillaries with hemorrhage and the liberation of fibrin. Although the condition is primarily interstitial, this heavy infiltration of blood and fibrin "pours" over into the alveolar spaces, lending bulk and the various color changes to the gross morbid appearance. It is often intense and in striking contrast to the few cells within the air sacs. The consolidation is the interstitial

exudate, plus this alveolar hemorrhage. Occasionally one may see small areas of hemorrhage with comparatively little or no cellular exudate and surrounded by air-containing tissue. Grossly these will appear as hemorrhagic foci without consolidation. They are apparently identical with the small hemorrhagic lesions described by Paul. Many of them show an inflammatory aspect, perhaps a few irregular epithelioid cells or an occasional small perivascular group. We would consider them to be a very mild, but definite expression of acute rheumatic pulmonary pathology.

Where phagocytosis of hemorrhage occurs, as evidenced by the appearance of large phagocytic monocytes, so-called "Herzfehler" cells, one may be confused as to whether there is a true inflammatory process or only passive congestion, especially since there may be coëxisting mitral stenosis. Case 3 (E.H.) in this connection is worthy of comment. The gross appearance of the lungs was certainly not that of passive congestion. The lesions were too localized; large portions of the lung tissue were comparatively anemic and the bases were fairly clear. The cellular infiltration was, of course, distinctly inflammatory, including large Aschoff cells. The presence of "Herzfehler" phagocytes must then be explained by the hemorrhagic character of the inflammation, which in acute rheumatic lesions is not uncommon and in this particular lesion, acute pneumonitis, is rather characteristic.

The above changes are the result of vascular damage in small bloodvessels—capillaries and arterioles. Endothelial hyperplasia to the point of complete occlusion of these small vessels, is now a recognized step in the development of a rheumatic lesion. The knowledge of vascular changes in this disease has recently been advanced by the recognition of intimal changes in the aorta and other large bloodvessels.²¹ Obliteration by the inflammatory process of a large artery, contributing to the formation of gross infarction, has not to our knowledge been previously described. Sudden occlusion of a large coronary artery in the course of rheumatic fever in a patient who recovered has been recently recorded. Such occurrence is rare.²²

In Case 5 (S.C.) and Case 9 (R.I.) large branches of the pulmonary artery were completely occluded by tissue that is distinctly inflammatory, identical with perivascular infiltration, which has spread through the vessel wall to reach the intimal surface. The intravascular infiltration exhibits numerous new capillaries and perivascular collections of endothelioid cells. There is presented, therefore, vascular occlusion by rheumatic arteritis with destruction of large areas of tissue, in contrast to a similar microscopic process that is going on constantly in the small bloodvessels in rheumatic fever. The development of infarction was aided, of course, by cardiac weakness which embarrassed the collateral circulation.

Inflammation of the trachea and bronchi was not noted in these cases. At least there was an absence of purulent changes in the

mucosa. The occasional reddening and swelling of the mucosa can be explained by the microscopic picture of peribronchial and intra-bronchial infiltration of cells, which are probably transported there by the lymphatics draining the pulmonary tissue. Sometimes the smaller bronchial branches were filled with blood. The rather mild changes in the bronchial tubes and the absence of gross lesions in the trachea, will lend some significance to the statements of clinicians that the pulmonary involvement in rheumatic fever, unlike bronchopneumonia, is not a result of upper respiratory tract infection. Rheumatic pneumonia, however, may be associated with other infections. Case 4 developed a rheumatic pneumonitis and a pneumococcic lobar pneumonia.

Singularly enough, the majority of these acutely inflamed lungs showed but few lesions of their pleural surfaces. There was occasionally a very mild dullness of an otherwise smooth surface. Small amounts of clear fluid were recovered from the pleural sacs. In Case 2 (F.R.) an exception as regards the pleural involvement was an adhesive pleuritis and mediastinitis, without consolidation of the lung tissue.

Eight of these cases exhibited a pericarditis. Case 2 (F.R.), without the consolidation, had a pericarditis; Case 3 (E.H.) on the contrary showed no pericarditis, but did have massive consolidation. Rheumatic pneumonitis and pericarditis usually coexist, but apparently need not always do so. All the subjects had some acute manifestation of cardiac rheumatism; all but 1 (Case 6, W.S.) had acute endocarditis.

The endothelioid reaction that is an essential feature in rheumatic pneumonitis is seen, as far as we know, in only one other condition in human pathology, and that is occasionally in subacute bacterial endocarditis. The histologist may, in such cases, find small perivascular groups of large cells, but that is only a trivial microscopic suggestion of what in rheumatic fever may proceed as far as the production of lobar consolidations. Ninety per cent of cases of subacute bacterial endocarditis show implantation of that condition on rheumatic carditis. Histologic changes in the lungs of such patients, therefore, may well be part of a rheumatic pathology. Experimentally this endothelioid reaction in lung tissue is seen constantly in rabbits following injections of the *Streptococcus cardioarthritidis*.²³ The gross appearance of rheumatic pneumonia (Fig. 1) bears a close resemblance to lungs consolidated in the course of *Streptococcus viridans* infection in young children. The histology of the latter infection likewise is suggestive, in some ways, of what is seen in rheumatic fever. Incidentally the presence of such an inflammatory reaction in lung tissue, in human pathology, disproves the contention that the endothelioid cells of the Aschoff nodule in heart muscle, are derived from muscle cells.²⁴

Summary. Nine cases of acute rheumatic fever are presented with reference to their pulmonary pathology. Eight of these show

an acute inflammation of lung tissue with consolidation; the ninth shows pleurisy with subacute lung involvement. All of them are associated with acute rheumatic heart disease. The inflammatory pulmonary reaction consists of an interstitial perivascular exudate of large endothelioid cells, identical in morphology with those found in rheumatic heart lesions and considered pathognomonic of rheumatic fever. Hemorrhage and fibrinous exudate are prominent features. We therefore consider that in many virulent cases a characteristic rheumatic pneumonia is to be found.

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ABDOMINAL CRISES IN SICKLE-CELL ANEMIA.

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In 1910 Herrick described peculiar poikilocytes which he found in the blood of an anemic negro. He applied the descriptive term sickle to these cells. Only 3 instances^{4,5,6} of this sickling phenom-

enon were observed and reported in the next 13 years. In 1923, however, with the appearance of papers by Sydenstricker² and Huck³ sickle-cell anemia was established¹ as a definite disease entity. Since this year an ever increasing number of articles in the literature has served to acquaint the medical profession with the general pattern of this malady. The articles of Emmel,⁷ Graham,^{8,9} Hahn,^{10,11} Josephs,¹² Rich,¹³ Moore,¹⁴ Anderson,¹⁵ and that of Landon and Lyman¹⁶ are especially noteworthy in this respect. With this array of available information set forth, there seems to be no need for our purposes to redraw the picture currently thought to represent sickle-cell anemia. In spite of the excellent observations made and reported, many features of this fascinating disease remain unexplained. Among these are the so-called abdominal crises experienced by some patients whose blood reveals sickle cells.

Recurrent abdominal pain is emphasized by all writers on sickle-cell anemia. Epigastric pain after eating and recurrent attacks of epigastric and left hypochondriac pain are noted in all reported protocols. Such episodes occur not infrequently during the disease's latent phase when the symptoms are few and the physical signs are only suggestive. During the active phase these attacks may occur more frequently and may be very severe. Vomiting may occur. In addition one may find at the same time some degree of abdominal tenderness with rigidity, fever and leukocytosis. Not infrequently the attacks simulate those occurring in the tabetic. This simulation is accentuated by the presence of leg ulcers and lymphadenopathy. The symptoms may be general, unilateral and upper or lower abdominal in location. The attacks may be acute enough to simulate gall stone colic, appendicitis, or a ruptured viscus and the need for an emergency laparotomy may seem to be imperative. The sickle-cell anemic patient may of course be the victim of such abdominal diseases; on the other hand, the surgeon may be disappointed in not finding an explanation for the patient's difficulties at the time of operation. It is not unlikely that sickle-cell patients have been subjected to needless laparotomies. Such experiences are not generally reported, due to the natural tendency not to publish diagnostic failures especially when the correct diagnoses have not been established. It is quite possible to miss mild degrees of sickling in the usual blood studies as they are made, especially when these have been limited to leukocytic counts. Graham's⁸ case had an appendectomy performed on a previous admission. One of Alden's¹⁷ cases was diagnosed either pneumonia or appendicitis, but fortunately the condition subsided before operation was performed. Hein's²² patient sought relief for epigastric pain. Smith's¹⁸ case presented symptoms suggestive of gall bladder disease with complicating appendicitis. The discovery of sickle cells in this patient's blood obviated the need for operative intervention. We have observed a patient who would undoubtedly have been

subjected to an abdominal operation but for the knowledge that his blood contained sickle cells. Two other patients with painful abdominal attacks are cited so that certain matters pertaining to the occurrence of abdominal crises in the course of sickle-cell anemia may be conveniently discussed.

Case Reports. CASE 1.—A male negro, aged 25 years, was first admitted to the Philadelphia General Hospital in October, 1926, because of severe pains in his arms and legs. A diagnosis of subperiosteal abscess of the right tibia was made, and the lesion was incised and drained. A culture of the puslike material obtained was sterile. The patient made an uneventful recovery and eloped from the hospital before the wound had completely healed.

In September, 1929, he was admitted for the second time because of pain in his legs and back. An attempt was then made to establish a diagnosis of congenital lues despite negative serologic findings in both the blood and spinal fluid. It was further noticed that he presented the picture of a hypopituitary disturbance. This suspicion was strengthened by an increased sugar tolerance and the findings on Roentgen ray examination of a sella turcica larger than normal with hazy and probably rarefied posterior clinoids. The basal metabolic rate was + 4 per cent, and the visual fields were normal. On discharge the final diagnoses were congenital lues with luetic periostitis and aortitis, congenital psychopathic inferiority, and hypopituitarism.

On January 1, 1930, the patient was admitted for the third time, complaining of severe pain in both shoulders and lumbar spine, and occasional vomiting and pains in the epigastrium after eating. This was the first time the patient was seen by us.

Physical Examination. The patient was a black male, aged 25 years, who appeared much younger, and distinctly under normal size. There were few positive findings. The tonsils were hypertrophied and diseased. The heart was enlarged to the left and right and a systolic murmur of moderate intensity was heard at the apex and at the first intercostal space to the right of the sternum. The blood pressure was 110 systolic and 62 diastolic in both arms. The extremities revealed a scar over the right tibia, the patient showed tenderness over both deltoid muscles, and exaggerated reflexes. The posterior and anterior cervical, the epitrochlear and inguinal glands were uniformly enlarged.

Laboratory Observations. The red blood cells varied from 2,400,000 to 3,300,000; hemoglobin 60 per cent to 80 per cent. The color index was + 1. The white blood cells varied from 10,900 to 19,400; the differential count was normal. Forty-four nucleated red blood cells were seen in counting 100 white blood cells. Anisocytosis, poikilocytosis, and polychromatophilia were found routinely. Sickle cells varied from 6 to 50 per cent in both the fresh preparations and the stained films. Reticulocytes varied from less than 1 to 5 per cent. Clotting time was $2\frac{1}{2}$ minutes and bleeding time 3 minutes. The platelets varied from 280,000 to 480,000. Hemolysis began at 0.30 per cent and was complete at 0.20 per cent salt solution. The blood sugar was 80 mg., blood urea nitrogen 12 mg., cholesterol 165 mg., calcium 10.4 mg., phosphorus 4.6 mg. per 100 cc. of blood, and blood pH was 7.44. The icterus index varied from 8 to 15; the Van den Bergh reaction was delayed. The urine showed a constant trace of albumin; the specific gravity varied from 1006 to 1008; urobilin was present; and 70 per cent elimination of phenolsulphonephthalein occurred in 2 hours. Gastric analysis on one occasion showed a free hydrochloric acid of 6; total acidity of 18; on another occasion 25 free and 60 total in terms of $\frac{1}{16}$ normal NaOH solution.

Roentgenologic Examination. The gall bladder was found normal by the intravenous dye test. Gastrointestinal Roentgen ray study showed no abnormalities except for increased colonic peristalsis. The heart was enlarged to the left and there was a considerable enlargement of the right auricle. The aorta was normal.

Skull. There was considerable thickening of the outer table of the parietal bone. This was due to new bone formation, showing as striations perpendicular to the long axis of the skull. The suture lines were indistinct.

Spine. The vertebrae were shortened in their vertical dimensions and somewhat widened in diameter. They had a soft appearance, there being considerable decalcification. The trabeculae were rather prominent and sharp and the cancellous spaces were rather large. (Fig. 1.)

Pelvis. The bones of the pelvis showed considerable osteoporosis. The trabeculae were rather sharp.

Ribs. The ribs were irregularly deformed. They had a soft appearance due to an osteoporosis. The cancellous structure was rather prominent. The scapulae were apparently not involved. The inner portion of the clavicles showed osteoporosis.

Left Foot. There was considerable osteoporosis. The trabeculae were sharp and had a pencilled appearance. There were a number of dense lines of bone condensation extending across the medullary cavity. These were particularly prominent in the lower end of the tibia. The cancellous spaces were rather large. (Fig. 2.)

The changes noted in the skull and the other bones were characteristic of the osseous lesions found in sickle-cell anemia.

Course. On many occasions during the patient's long stay at the hospital he was seized with severe abdominal pain, at times localized in the upper quadrants and at other times in the lower quadrants. These critical attacks were accompanied by nausea, vomiting, rigidity, diminution of peristaltic sounds, and generally with fever up to 102° F. The agony was so excruciating that the patient assumed all kinds of bizarre positions, at times extreme opisthotonos. Frequently these attacks were accompanied by pain in the back, thighs or lower chest. Morphine sulphate in large doses at short intervals was necessary for relief of the pain. Diagnosis of appendicitis, cholecystitis, pancreatitis, peritonitis and Pott's disease were made by those who saw him during attacks. Surgeons who were consulted advised against operation on a number of occasions, chiefly because of the sickle-cell features observed in the patient.

CASE 2.—A colored girl, aged 23 years, was admitted to the Philadelphia General Hospital on September 6, 1929, to the service of Dr. Herman B. Allyn. Since the age of 10 the patient had been in poor health and complained of generalized joint and extremity pains and frequent sore throats. At the age of 18 she had a long siege of acute rheumatic fever, but her doctor had diagnosed heart disease a few years before this attack. On several occasions she had edema of the ankles.

Physical Examination. The patient was a black female, aged 23 years, poorly developed, poorly nourished and dyspneic. The tonsils were hypertrophied and diseased. The submaxillary glands were enlarged. There was a marked, diffuse precordial pulsation. The apex beat was in the seventh interspace at the anterior axillary line and precordial dullness extended from beyond the right border of the sternum to the axilla. A rough presystolic and a blowing systolic murmur was heard over the entire precordium and was transmitted to the back. The second pulmonic sound was louder than that of the second aortic. The blood pressure was 110 systolic and 75 diastolic. The liver was enlarged to 4 inches below the costal margin and the spleen was easily palpable.



FIG. 1.—Case 1. The vertebræ are shortened in their vertical dimensions and somewhat widened in diameter. They have a soft appearance, there being considerable decalcification. The trabeculæ are rather prominent and sharp and the cancellous spaces are large.



FIG. 2.—Case 1. Left foot. There is considerable osteoporosis. The trabeculae are sharp and have a pencilled appearance. There are a number of dense lines of bone condensation extending across the medullary cavity. These are particularly prominent in the lower end of the tibia. The cancellous spaces are rather large.

Laboratory Observations. The red blood cells varied from 1,950,000 to 2,700,000; hemoglobin from 40 to 62 per cent. The color index was +1. The white blood cells varied from 7600 to 13,700 and the differential count was normal. Anisocytosis, poikilocytosis, polychromatophilia and nucleated red blood cells were present on all examinations. Sick cells varied from 3 to 20 per cent on the stained films. Hemolysis began at 0.46 per cent and was complete at 0.22 per cent salt solution. The blood sugar was 76 mg. and the blood urea nitrogen was 12 mg. per 100 cc. of blood. The icterus index was 12 and the Van den Bergh reaction was delayed. The urine showed a trace of albumin and the specific gravity varied from 1009 to 1012. The electrocardiogram revealed flattened *T* waves in Lead I and inverted *T* waves in Lead II. The *Q-R-S* complexes in Lead I were notched. The roentgenogram of the chest showed considerable pulmonary congestion of both lung bases. There was general cardiac hypertrophy; the heart apex being in the left axilla, and the left auricle much enlarged. The contour of the heart suggested a double mitral lesion with a probable pericarditis. The vertebrae and ribs as shown on a film taken primarily for cardiac study showed no unusual bony lesions.

Course. The patient died 5 months after admission to the hospital. During this time she had frequent episodes of severe lower and upper abdominal pain which were relieved with difficulty only after repeated administrations of morphin.

CASE 3.—A colored female child, aged 4 years, was first admitted to the pediatric service of the Philadelphia General Hospital on September 12, 1929. She was a normal baby at birth weighing 7 pounds, 6 ounces. At the age of 4 months she developed rickets and since 2 years of age she had been suffering from anemia, attacks of fever, anorexia, vomiting, pain in the abdomen, back, head and legs. At first these attacks occurred about 1 month apart, but recently they had occurred more frequently. The attacks had often been ushered in by convulsions and a comatose state, suggestive of epilepsy. In the past 2 years she had had a tonsillectomy and several blood transfusions.

Physical Examination. The patient was an anemic, undernourished black girl, aged 4 years, very restless, tossing about, with her legs drawn up. The temperature was 103° F., and the pulse was 120 per minute. Her head was large, flat, and square. The tonsils had been removed. The chest revealed a rachitic rosary. The heart was enlarged to the left and the blood pressure was 130 systolic and 100 diastolic. The spleen was enlarged 4 inches below the costal margin; the liver was not palpable. A small umbilical hernia was present. The cervical and inguinal glands were hypertrophied.

Laboratory Observations. The red blood cells varied from 1,500,000 to 3,800,000; hemoglobin from 40 to 60 per cent. The color index was usually above 1. The white blood cells varied from 4000 to 39,000; of which 40 to 60 per cent were polymorphonuclear leukocytes. Anisocytosis, poikilocytosis, and polychromatophilia were routinely present. Nucleated red blood cells were usually present in varying numbers. Reticulocytes were found ranging from 2 to 10 per cent. Sick cells varied from a few to very many on the stained films. Clotting time was 3½ minutes and bleeding time 1½ minutes. The platelets varied from 160,000 to 520,000. The blood sugar was 111 mg.; blood urea nitrogen, 16 mg.; calcium, 12.7 mg.; and phosphorus, 4.4 mg. per 100 cc. blood. The spinal fluid Wassermann and blood cultures were repeatedly negative. The von Pirquet test was also negative. The urine showed a trace to a heavy cloud of albumin, occasional granular and many hyaline casts, and a low fixed specific gravity varying from 1003 to 1007.

Roentgenologic Examination. The skull Roentgen ray showed evidence of cerebral atrophy due to intracranial pressure and the typical perpendicular striations of the outer cortex characteristic of sickle-cell anemia. The chest plates showed enlarged glands in the right hilum shadow. The diaphysis of both femora and both tibiae were widened and the zone of ossification denser than normal, suggestive of healed rickets. Roentgen ray studies of the spine showed nothing unusual.

Course. From September, 1929, to April, 1930, the patient was admitted to the hospital three times. The critical abdominal attacks, accompanied by fever, vomiting, leukocytosis and pains in the head and extremities were always relieved by blood transfusions. The true nature of the disease was however, not appreciated since sickle cells were either absent on the blood films or were not noticed. The final diagnoses were hilum tuberculosis, chronic diffuse nephritis with acute exacerbations and uremic convulsions, brain tumor, rickets, congenital lues with splenomegaly, anemia, and malnutrition.

On the fourth admission in May, 1930, the diagnosis of sickle-cell anemia was made. A splenectomy was performed by Dr. Eliason on July 1, 1930. This was followed by a good operative recovery and a temporary improvement of the patient's symptoms.

Pathologic Report of the Spleen. The spleen weighed 200 gm. and was of elastic consistency. The surface was irregular because of superficial scars and the capsule overlying the scars was thickened and opaque. The cut surface had a glistening deep red appearance, and the follicles could be distinguished only with difficulty. On microscopy the striking appearance was the extreme congestion. The Malpighian follicles were enlarged and some of them displayed endothelial hyperplasia. Although there was some thickening of the capsule there was but little diffuse fibrosis.

Further Course. Two months after the splenectomy the patient returned to the hospital suffering with the same symptoms that she had had for the past 3 years; namely, headache, back and extremity pains, abdominal rigidity and pain, vomiting and fever. These symptoms were again relieved temporarily by blood transfusions. There have since been two more admissions for similar complaints. The removal of the spleen in this patient has apparently failed either to modify the course or character of the disease or to relieve the distressing abdominal attacks.

Comment. These 3 patients illustrate the salient characteristics of sickle-cell anemia, and more particularly its variable abdominal symptomatology. Our third patient was temporarily relieved by blood transfusions which would suggest that the anemia *per se* may be responsible for the critical episodes under consideration. Any discussion, however, of such abdominal attacks must take into consideration that the disease is notable for its remissions and relapses. Under such circumstances there is no justification in rationalizing a treatment on the favorable outcome of a therapeutic procedure. If any conclusions are to be drawn after the practice of a therapeutic test, the results should be reasonably permanent, constant and clearly related to the treatment. This is not true for our patient and it has not been so for other patients as reported in the literature. The term sicklemia has been suggested instead of sickle-cell anemia because a grave anemia is not constantly found in these patients. It is perhaps best reserved for

those cases that show sickling without anemia. While our 3 patients presented a severe anemia at times, still the abdominal attacks did not necessarily coincide with the periods of marked hemoglobin and red cell depression.

In the matter of remissions and relapses sickle-cell anemia resembles primary anemia, although it differs from this disease in many details. Patients suffering from pernicious anemia seldom have abdominal pains. Baily²⁰ observed 2 cases of acute abdominal crises in the late stages of pernicious anemia. He operated on the first one and found no lesions aside from a distended gall bladder filled with so-called "biliary mud." Explanation is made to the effect that the liver because of a sudden great blood destruction must secrete large amounts of pigment in a concentrated form and this in turn accumulates in the gall bladder. The weakened patient responds strongly to this painful stimulus. Such a condition has not been found in sickle-cell anemia and therefore can hardly explain the frequent abdominal attacks in sickling patients. It must also be a very rare occurrence in pernicious anemia. Taking, then, all of these comments into consideration it would seem that the anemia of sickling patients is not accountable for their abdominal pains.

The disease resembles hemolytic jaundice in some ways. Sickle-cell anemia is like acholuric jaundice in its hereditary nature, jaundice, blood picture, evidence of blood destruction, relapses and remissions; but differs, in that it seems to be confined to the negro race, shows sickle cells, the atrophic, scarred spleen of older patients, the leg scars, the joint pains, abdominal crises and the failure of splenectomy to cure the condition. Although the hemolytic jaundice patient may have abdominal pains during a severe exacerbation, these attacks are not comparable to those we have observed in sickle-cell anemia. The abdominal pains occurring in the latter disease impress one as being the same sort of pain which is experienced in the extremities and these are absent in the presence of hemolytic jaundice. It must seem apparent to those who have given thought to the matter that the hemolytic features of sickle-cell anemia are not accountable for the critical abdominal attacks.

The pains under consideration may or may not occur in patients with a variable or a constant number of sickle cells. Hahn¹¹ believes there is a correlation between the severity of sickle-cell anemia and the number of sickle cells in the circulating blood. He further found that symptomless individuals with the sickle-cell trait have few or no sickle cells in the circulating blood. In our first patient, however, studies made of quickly dried smears showed no appreciable variation in the number of sickled cells both in and out of abdominal attacks. It is difficult to estimate the amount of sickling present inasmuch as wet preparations show an increasing number of deformed cells, up to 100 per cent, as time elapses after blood

withdrawal.²³ There is some question as to whether the bizarre forms which are found after a wet preparation stands for a time are identical with those found in blood immediately after the blood has been taken. We have a feeling that examination of a dried smear is the best method of studying sickling quantitatively. On the other hand one is less likely to overlook the presence of sickle cells in doubtful patients by the examination of wet preparations at varying intervals after the blood has been withdrawn. All negro patients should receive the benefit of study in the latter way especially so when they present abdominal symptoms and operation is contemplated.

Hahn^{10,21} has shown that the saturation of the blood with CO₂ will produce sickling and that the sickle cells will return to the round form if the blood is then saturated with oxygen. He therefore suggests that anoxemia may be a factor in the production of the sickle-cell distortion in living subjects. With this in mind, our first patient was placed in an oxygen tent during an attack. This procedure did not seem to influence the intensity of his pain or the degree of sickling.

Sydenstricker²³ found that reduction of the blood pH *in vitro* to 7.3 or 7.25 causes immediate sickling. During a symptom-free period in our first patient we tried to produce an attack by the administration of massive doses of ammonium chlorid as well as by feeding a ketogenic diet. As a part of the experiment we also gave the same patient at other times large doses of sodium bicarbonate. These therapeutic trials produced no appreciable change in the patient's condition and were unaccompanied by any change in the degree of sickle-cell formation. While many things seem to influence the amount of sickle cells observed *in vitro*, nothing has been suggested that changes the picture *in vivo*. The administration to our first patient of bicarbonate of soda and potassium citrate together with potassium sulphocyanate was followed on two occasions by an immediate cessation of attacks but no difference in the sickle-cell count. Thus far then, it would seem on the strength of our observations that the mere presence of sickle cells in the circulating blood does not account for the painful episodes.

Inasmuch as the abdominal pains simulate gall bladder attacks on occasions, the question arises as to whether this organ may not be the responsible agent for the abdominal picture under discussion. Hamilton²¹ described a case of sickleemia complicated by gall stones, but Hein²² noted gall stones in only 3 of 12 patients. Our first patient yielded normal cholecystographic studies. Normal gall bladders have been observed in "sicklers" at autopsy who have had attacks of severe pain and rigidity in the upper right quadrant of the abdomen, accompanied by jaundice, vomiting, shoulder and back pain, fever and leukocytosis. This suggests the difficulty of making a decision for or against the presence of gall bladder disease. Yates and Mollari²⁷ reported a patient who died during an abdomi-

nal crisis as the result, they believed of an arterial thrombosis in the liver. There was however insufficient evidence to substantiate this point. This finding has not been previously reported in sickle-cell anemia and could hardly therefore be counted as the usual cause for the pains with which we are concerned. It would seem then, that the evidence tends to exonerate both the liver and gall bladder as being the usual factor in abdominal pain production for these patients. While the liver is uniformly the seat of pathologic lesions at autopsy, this is not true in the large majority of gall bladders examined at such a time.

Sydenstricker¹⁹ suggests that the usual hypochlorhydria present in this disease may account for some of the gastric manifestations. In the population generally, many individuals present hypochlorhydric states of a like degree but certainly do not have pains which are only relieved by morphin as was true of our first 2 patients.

In addition to morphin, atrophin sulphate, adrenalin hydrochlorid and nitroglycerin were tried hypodermically for our first patient. Calcium and distilled water intravenously also were used.

Many drugs were given by mouth, including the salicylates, and a liver diet plus various liver preparations. None of these therapeutic efforts made an appreciable difference in the severity of the pains. On several occasions it was thought that sterile water hypodermics gave relief, but this was not true during many other attacks. During the remission phases this patient asked for no medication. This seemed to controvert a thought entertained by some that he was experiencing some morphin withdrawal effects. During attacks there was no change in the arterial blood pressure. Whether the pains are a manifestation of some bloodvessel phenomenon, some automatic nervous system disturbance, an allergic state, or some unsuspected condition, must remain an open question. If they are due to one of the above conditions then it would seem that we should have produced some effect by our numerous medicinal practices.

The infarctive¹⁹ and hemorrhagic¹⁷ accidents occurring in the spleen may account for some of the pains. Splenectomy has been performed in a number of sickle-cell patients^{10,11,16,24,25,26} with a general but not a uniform improvement in the anemic state. No one has observed a favorable influence on the sickling phenomenon after splenectomy. If the splenic accidents are responsible for the abdominal attacks then we must seek further for an explanation of the very similar chest and extremity pains. Painful abdominal attacks will occur even after splenectomy, as is shown in our third patient who had this operation performed in July, 1930. She was admitted 2 months later because of the recurrence of abdominal pain. Such an experience would indicate clearly that the spleen is not to blame for all of the abdominal symptoms under discussion.

Because of the findings on Roentgen ray examination of definite and extensive lesions in the spine of our first patient, it occurred

to us that the paroxysmal crises in sickle-cell anemia may have their primary origin in these bony lesions. The pains resemble, in a measure, those of root origin as they are found in patients with other vertebral diseases. As far as we are able to determine, no one has carefully studied the nervous system of such patients. The bones of the extremities and skull are not tender nor does the pain seem to be seated in the osseous system. It would seem then that the bony changes as observed by the Roentgen ray are not of themselves responsible for the symptoms complained of by these patients. If not of root origin then the abdominal, extremity and chest pains occurring in our patients may be comparable to the crises of syphilis. In any event, if these pains are not, as they seem to be, of visceral or bony origin, they must be of nervous origin.

Our third patient showed no vertebral Roentgen ray changes and the same is probably true for the second patient as reported. It is quite possible, in spite of these negative findings, that the pains with which we are concerned are nevertheless of a neurologic nature. While muscular rigidity such as was exhibited by our patients is usually due to a visceral lesion still it may result from a so-called "intercostal neuralgia." Carnett^{28,29} reported 6 cases of extensive abdominal pain, tenderness and rigidity in the absence of an intra-abdominal lesion. In his numerous contributions on the subject of "intracostal neuralgia" he has shown that "nerve irritation in spinal arthritis is due to an inflammatory exudate in the intervertebral foramina or in the epidural space pressing on the spinal nerves or their roots. This early inflammatory exudate may subside in the later stages with disappearance of sensory symptoms or it may undergo organization with prolongation of symptoms. The extent of bone changes by the Roentgen ray is not an index of the severity of the referred sensory symptoms." While the bony lesion of sickle-cell anemia patients is not inflammatory in nature it is quite possible that the sensory phenomena exhibited by our sickling patients may have a production mechanism similar to that offered in explanation for the spondylitic, even in the absence of Roentgen ray evidence of bone disease.

It is quite probable that the critical episodes occurring in sickle-cell anemia will remain unsatisfactorily explained as long as we are ignorant concerning this disease's causation. Graham theorizes that since these subjects are peculiarly liable to tonsillitis, as was true for our patients, the intermittent attacks may be due to a lighting up of an infective focus. This would explain, he believes, why recurrences take place so frequently after exposure to cold. He further recalls that phagocytosis in the blood by endothelial leukocytes is known in acute and chronic sepsis and especially in infections by the streptococcus. The kidney lesions in this disease are like those produced by the streptococcus. To this we might add that the temperature elevation and leukocytic blood count suggest a microorganismal origin for the disease although no positive blood

cultures have thus far been reported. It may then develop that the pains under discussion are nothing more than the so-called toxic pains which occur in the course of many infectious diseases. They are however peculiarly severe in sickle-cell anemia, if they have such an origin.

Summary and Conclusions. 1. Three patient reports of sickle-cell anemia are presented to illustrate the critical abdominal attacks which may occur in this disease.

2. Current explanations of such paroxysmal abdominal pains as found in the literature are discussed.

3. Other explanations not previously suggested are examined.

4. None of these, whether old or new, are thought to explain adequately the abdominal crises under consideration. It is quite possible that a single explanation may not apply for all of the critical abdominal episodes as they occur in sickle-cell anemia. On the basis of marked bony changes in the vertebræ of our first case we have suggested root pains as a cause for the paroxysmal crises of pain and rigidity.

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UNILATERAL OPACITIES IN CHEST FILMS.

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THE differential diagnosis of unilateral opacities in chest films offers considerable difficulty because a similar shadow can be produced by many causes.

Careful analysis of the symptoms, together with physical signs and laboratory methods, often gives one sufficient data upon which to base a diagnosis; but the Roentgen ray interpretation often gives the convincing clue as to the exact condition present.

There are certain conditions in the chest which with our present knowledge can only be recognized by biopsy, and at times only by autopsy. Such methods as proper positioning under the Roentgen ray, bronchography and more frequent bronchoscopies have aided us considerably in clearing up many otherwise puzzling problems.

The physical conditions of the chest which may produce opacities in the Roentgen ray film are as follows: Tumors of the chest wall, fluid in the pleural cavity, tumors of the pleura, atelectasis of the entire lung, pneumonia, tuberculosis, many other massive infections of the lung and marked pleural thickening or fibrosis.

It is the purpose of this paper to demonstrate the ease with which the observer may often solve the problems incident to interpreting unilateral opacities if he makes use of all methods of diagnosis.

Case Reports. CASE 1.—*Mediastinal Tumor (Hodgkin's Disease) with Pleural Effusion.* C. C., a woman, aged 24 years, was admitted to the Barnes Hospital, February 20, 1930, with a history that since October, 1929, she had lost strength and had suffered sharp stabbing pain in the right upper chest associated with cough. An afternoon rise in temperature (101° F.) was noted in November, 1929. The pain increased in severity, dyspnea appeared and the patient was admitted to the Missouri Baptist Hospital, January 16, 1930. On February 1, 1930, her face, arms and neck began to swell. Because the presence of fluid was suggested by a Roentgen ray film, an attempt was made anteriorly to withdraw it. A small amount of pus was obtained, probably from a bronchus. Aspiration in the right axillary line yielded serous fluid.

Upon admission to the Barnes Hospital it was noted that the patient had marked swelling of the face, neck and right arm. She was orthopneic and rather pale. Her blood pressure was 108 systolic and 68 diastolic, the same in both arms. Physical findings were all referable to the right chest. On questioning it was found that she also suffered from sternal tenderness and general itching. Her leukocyte count was 18,900, with a relative preponderance of polymorphonuclear cells (90 per cent); there was no eosinophilia. Laboratory findings were negative.

Aspiration of the chest in the right midaxillary line on February 21 yielded

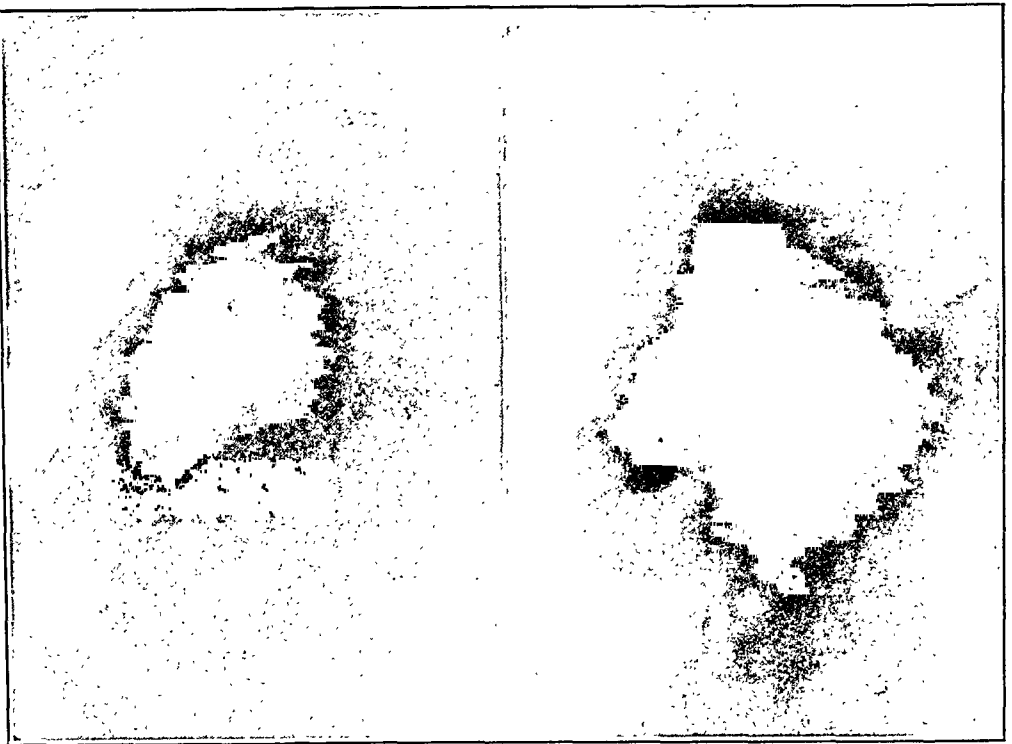


FIG. 1, *a*.—February 24, 1930. Unilateral opacity in the right chest from the first anterior rib which merges with the shadow of the liver. The heart and upper mediastinum are pushed toward the left. There is compensatory air content in the left lung.

FIG. 1, *b*.—February 24, 1930. Film taken after the aspiration of 400 cc. of clear fluid and the replacement by 100 cc. of air (diagnostic pneumothorax). A dense mass is now visible and a fluid level at the base is noted. The patient was slightly rotated to exaggerate the shadow. Diagnosis: Mediastinal tumor, probably Hodgkin's disease or lymphosarcoma.

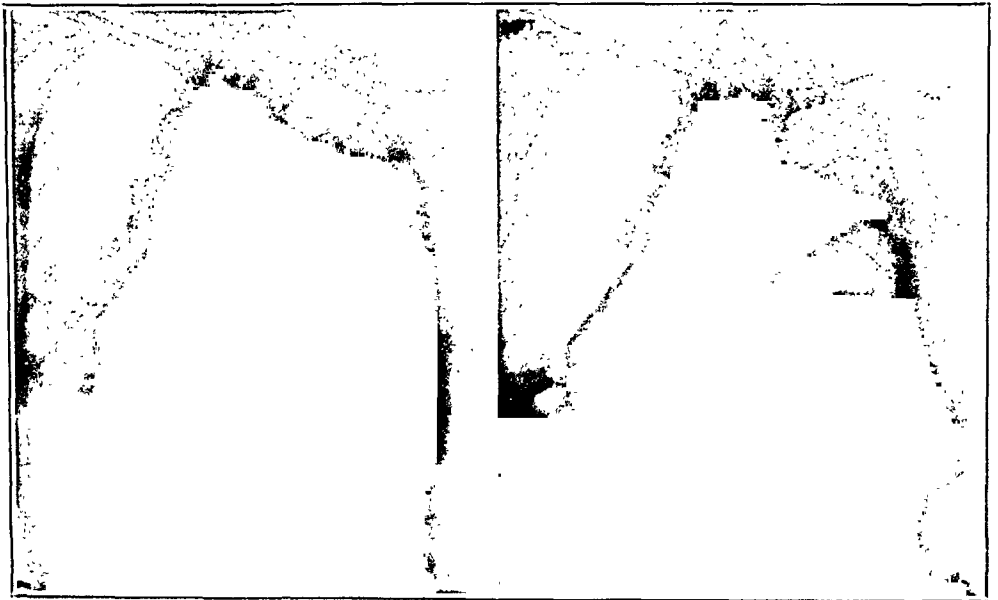


FIG. 2, *a*.—February 23, 1924. The Roentgen ray film shows a unilateral opacity in the right chest from the first rib and merging with the shadow of the liver. (Note similarity of Fig. 1, *a*.)

FIG. 2, *b*.—February 23, 1924. Film taken after the aspiration of 400 cc. of fluid and the replacement of 100 cc. of air. Note the dense mass made by visible the diagnostic pneumothorax. Note the fluid level. It is evident from this study that a distinct tumor is present in the right lung. (This was later proven by operation.)



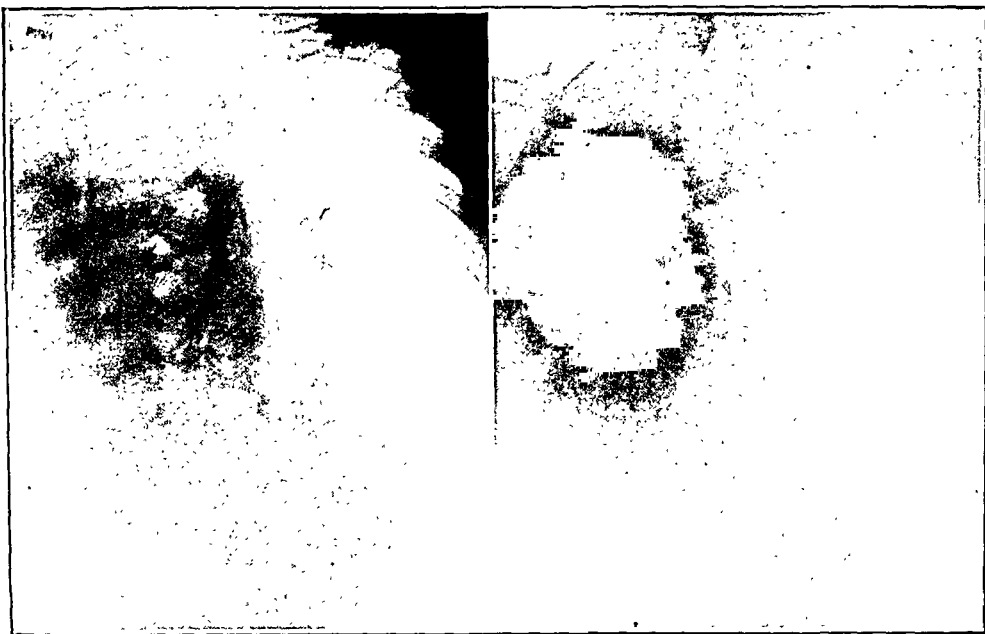
FIG. 3, a.—January 28, 1930. Unilateral opacity of the entire right thorax. No lung detail is noted. The left lung is normal. No definite diagnosis could be made, although many possibilities were suggested. A diagnostic puncture was made, pinkish-yellow fluid resembling pus was withdrawn and 100 cc. of air were introduced; a small amount of iodized oil was also introduced into the pleural cavity.

FIG. 3, b.—January 31, 1930. Film taken with the patient lying with the right side up. The diagnostic pneumothorax shows the presence of a large encysted collection of fluid and a smaller one below (this is well outlined with lipiodol). At operation a large cyst was noted in the right pleura, but no hooklets (*echinococcus*) were found. Diagnosis: *Echinococcus* (?) cyst or amœbic abscess. (Should be viewed horizontally with right side up.)



FIG. 4, a.—October 30, 1928. Unilateral opacity of the entire left side. Note the deviation of the trachea (left). No cardiac shadow is seen in the right side. The physical signs suggested fluid and aneurysm. Diagnosis: Massive collapse due to obstruction of the main left bronchus.

FIG. 4, b.—December 10, 1928. Lipiodol shows complete obstruction of the main left bronchus. Note the visibility of the vertebrae as a result of the retraction of the left lung. Autopsy disclosed rupture of aneurysm of the aorta and massive atelectasis of left lung probably from compression of left main bronchus.



a

b

FIG. 5, *a*.—June 6, 1929. Lipiodol introduced by the aspiration method shows the trachea and the main right bronchus dilated, the upper bronchus blocked, the middle partially and the lower one completely. The left bronchial tree is normal. There is some oil in the stomach. Diagnosis: Pulmonary tuberculosis with fibrosis and partial atelectasis of the right lung.

FIG. 5, *b*.—September 9, 1929. Unilateral opacity of the right lung. Note the deviation of the trachea to the right. Below the right clavicle there is a crescentic-like area of rarefaction. The right diaphragm is not visible. The left lung shows compensatory air content. The cardiac shadow is retracted to the right. Impression: Pulmonary tuberculosis with fibrosis of the lung.



a

b

FIG. 6, *a*.—January 20, 1930. Unilateral opacity of the entire right chest. Heart displaced to the left. No pulmonary markings noted. Signs of fluid. An aspiration showed a large amount of purulent fluid.

FIG. 6, *b*.—February 5, 1930. Film of patient after thoracostomy and drainage. The lung is partially expanded. Surgical pneumothorax (Dakin tubes in place). The heart has returned to its proper position. Diagnosis: Empyema, right pleura.



a



b

FIG. 7, *a*.—March 6, 1930. Photograph taken before the operation, showing edema of face and arms.

FIG. 7, *b*.—March 21, 1930. Photograph showing the condition after the *decompression* operation. Note the diminution of the swelling, also the scar.

1200 cc. of thin straw-colored fluid. The laboratory findings were negative. There were repeated aspirations. A diagnostic pneumothorax was done.

Roentgen ray examination: (Fig. 1, *a*.) February 24, 1930: Unilateral opacity in the right chest from the first anterior rib which merges with the shadow of the liver. The heart and upper mediastinum are pushed toward the left. There is compensatory air content in the left lung. Fig. 1, *b*, film taken, February 24, 1930, after the aspiration of 400 cc. of clear fluid and the replacement by 100 cc. of air (diagnostic pneumothorax). A dense mass is now visible and a fluid level at the base is noted. The patient was slightly rotated to exaggerate the shadow. Diagnosis: Mediastinal tumor, probably Hodgkin's disease or lymphosarcoma.

The diagnostic pneumothorax disclosed a dense mass (Fig. 1, *b*), apparently mediastinal, with collapsed right lung and free fluid in the pleural cavity. After the aspiration of 300 to 500 cc. of fluid the edema of the face, neck and arm diminished. It was, therefore, presumed that there had been definite compression of the superior vena cava.

After the analysis of the signs, symptoms and Roentgen-ray studies the following diagnoses were considered: (1) Mediastinal tumor, Hodgkin's disease; (2) serofibrinous pleurisy, tuberculosis; (3) atelectasis of the lung due to fibrosis; (4) endothelial tumor.

As the shadow in the right chest was homogeneous, the question arose whether the lung or the pleura was involved. Only a small part of the injected iodized oil entered the right bronchial tree because in all probability there was a pathologic compression of the main bronchus. Confirming this probability was the presence of fluid in the pleura. The blood picture was somewhat suggestive of Hodgkin's disease. The aspirated fluid was centrifuged, but no tumor cells were found. The sputum was consistently negative for tubercle bacilli. No glands were palpable for biopsy.

Deep Roentgen ray therapy was started on February 24 and was continued at intervals of several weeks. As the mass did not disappear after several Roentgen ray exposures and the dyspnea and cyanosis became alarming, it was decided to do a decompression of the anterior right chest. Dr. Evarts Graham removed portions of the second and third right costal cartilages. When the mediastinum was exposed a large firm, slightly gray, nodular mass was found firmly attached to structures within the chest wall and presenting all the characteristics of a malignant tumor. The diagnosis of a small portion removed for microscopic examination was Hodgkin's disease. Following the operation the edema of face, neck and hands disappeared and the patient steadily improved. The question arose as to whether the Roentgen ray treatment or the decompression produced this change.

Following the operation, the wound healed promptly and the patient improved remarkably. She was discharged from the hospital, March 25, 1930, and has returned from time to time for observation and Roentgen ray treatment. Improvement was marked for 7 months, at which time metastasis occurred in the right chest wall involving the 3 lower ribs.

In the light of all the clinical data, a diagnosis of tumor of the mediastinum (Hodgkin's disease) was made. A study of the Roentgen ray films shows how much information may be obtained by a diagnostic pneumothorax. (Fig. 7, *a* and *b*.)

CASE 2.—*Carcinoma of the Left Lung With Metastasis to the Ilium*. C. S., a woman, aged 65 years, was admitted to the Barnes Hospital, February 23, 1924, with a chief complaint of pleurisy on the right side.

In November, 1923, her right ankle was swollen for 1 week. She also noted at that time a dull pain at the right waistline which lasted 2 weeks. She suddenly became dyspneic and went to bed. There was no fever, cough nor pain in the chest, but the pain at the waistline persisted. On

December 9, 1923, the patient was taken to a hospital after an aspiration showed the presence of serous fluid. Several thoracenteses were performed; each time 500 to 1000 cc. of similar fluid were obtained. All the patient's Roentgen ray films taken in December before leaving the hospital showed a right unilateral opacity of almost the whole right chest. Three weeks before admission to Barnes Hospital a "hacking" cough had developed, but the dyspnea was better. A week later her right leg was painful when walking. She had a poor appetite and lost 20 pounds in weight.

The physician signs at the time of admission showed flatness and absent breath sounds in the right chest with compensatory sounds in the left lung. The heart was not displaced.

Roentgen ray examination: (Fig. 2, a.) February 23, 1924: The Roentgen ray film showed a unilateral opacity in the right chest from the first rib and merging with the shadow of the liver. (Note similarity of Fig. 1, a.) Fig. 2, b, a film taken, February 23, 1924, after the aspiration of 400 cc. of fluid and the replacement of 100 cc. of air. The dense mass made visible by the diagnostic pneumothorax and a fluid level were noted. It is evident from this study that a distinct tumor was present in the right lung. (This was later proven by operation.)

In order to establish the factors producing the dense shadow a thoracentesis was done, followed by a diagnostic pneumothorax. A fluoroscopic examination was then made. By viewing the patient in the lateral, upright and inverted positions, the injected air made it possible to outline a tumor mass in the midportion of the right lung.

A clinical diagnosis of questionable malignancy of the lung was made on the following data: Age, duration of disease, absence of fever, general weakness and signs of metastasis in the ilium.

Discussion. The probable diagnosis before the aspiration and the pneumothorax were done was similar to Case 1, that is, a massive tumor of the chest with fluid in the pleura. After the air was introduced the probability of a lung abscess or lung tumor was considered. The lesions in the liver and right ilium suggested metastases. An operation disclosed a mass in the right lung, a section of which showed this to be a bronchogenic carcinoma.

This case also shows how a diagnostic pneumothorax may help in the interpretation of the Roentgen ray film.

CASE 3.—*Cysts of the Right Pleura (Echinococcus or Amœbic?)*. J.W., a man, aged 41 years, was admitted to the Barnes Hospital, January 28, 1930, with the following complaints: Pain in the right chest, productive cough, shortness of breath, weakness, loss of weight and nightsweats.

The significant points of his past history were as follows: At about 12 years of age the patient worked in a slaughter house after school for a period of 2 years. At that time he had repeated attacks of diarrhea and occasional attacks of sore throat. He had three attacks of "quinsy" and had occasional attacks of pain in the right shoulder, radiating anteriorly around the chest and localizing in the right upper quadrant. Vomiting without nausea had occurred at intervals of 1 to 2 weeks for many years. In August, 1928, he was jaundiced for a period of several weeks.

His present illness began in January, 1929, with severe attacks of pain in the right shoulder, radiating to the right upper quadrant associated with jaundice. He was sent to a hospital, where a tentative diagnosis of carcinoma of the liver, cholecystitis and cholelithiasis was made. At operation the gall bladder and appendix were removed. No stones were found in the gall bladder, however, and this organ did not seem definitely diseased. For some time following the operation jaundice persisted and the patient still complained of pain in the right upper quadrant. Convalescence was otherwise uneventful and the patient returned to his home.

In June, 1929, his symptoms—cough, productive of white sputum, night-sweats and weakness—became more marked, and he developed a sudden sharp pain in the lower chest. He reentered the hospital, where evidence of fluid in the right pleural cavity was found. A thoracentesis was performed and about "1 gallon of pink-colored fluid" was obtained. Several other thoracenteses were performed; large amounts of fluid were withdrawn. The patient stated that this fluid was of a dark reddish-brown color. After 2 weeks in the hospital he was discharged. During the following months his symptoms were slightly improved.

In November, 1929, the patient had another attack of "quinsy" and in the same month had a tonsillectomy. About Christmas time all his symptoms became aggravated. Two weeks before admission to the Barnes Hospital his family physician attempted a thoracentesis, but no fluid was obtained; a second attempt was made with success. At the time of admission to Barnes Hospital the positive physical findings were flatness on percussion over the entire right chest, diminished breath sounds and diminished and absent vocal fremitus over the same area. The heart was moderately displaced to the left. There was harsh compensatory breathing over the entire left chest. No râles were heard. The abdomen showed a right rectus scar. There was tenderness along the right costal margin and the liver was palpable 2 finger breadths below the costal margin on the right.

Roentgen ray examination: (Fig. 3, a.) January 28, 1930: Unilateral opacity of the entire right thorax. No lung detail is noted. The left lung is normal. No definite diagnosis could be made, although many possibilities were suggested. A diagnostic puncture was made, pinkish-yellow fluid resembling pus was withdrawn and 100 cc. of air were introduced; a small amount of iodized oil was also introduced into the pleural cavity. Fig. 3, b, film taken, on January 31, 1930, with the patient lying with the right side up. The diagnostic pneumothorax shows the presence of a large encysted collection of fluid and a smaller one below (this is well outlined with lipiodol). At operation a large cyst was noted in the right pleura, but no hooklets (echinococcus) were found. Diagnosis: Echinococcus (?) cyst or amœbic abscess.

Discussion. The history and physical signs suggested an empyema following the gall bladder operation. This condition may or may not have been associated with a pulmonary abscess or subphrenic abscess, although there was no sputum for several weeks.

The history of long-standing diarrhea with bloody discharges, and the fact that amœbæ were found in the stool, suggested an amœbic abscess of the liver with secondary involvement of the pleura. The complement fixation test for echinococcus infection was 2+ on two occasions. Because of the similarity of the signs and symptoms of echinococcus and amœbic infections we were in doubt of the diagnosis. A Casoni test was negative. Treatment with emetin was instituted.

CASE 4.—Aneurysm Compressing the Left Bronchus (Massive Atelectasis). J. S., a man, aged forty-eight years, was admitted to the Barnes Hospital on December 4, 1928, complaining of pain over the heart, shortness of breath, loss of 20 pounds of weight and a cough. The patient gave a history of having always been well until about June, 1928, when he noticed he was short of breath; however, he had previously noted a "neuritis" across the upper back and shoulders which was aggravated by exertion. Two months before entering the hospital he had some pain over the region of the heart, which gradually became worse. Just 10 days before admission a cough which seemed associated with the pain over the heart was noted and the sputum was frequently blood streaked.

Physical findings upon admission showed a tracheal tug, and the chest examination showed the left side to be smaller and the movements less

than on the right; physical signs showed evidence of compression of the bronchi of the left lung and fluoroscopy and Roentgen ray films showed a high immobile left diaphragm with density throughout the left lung field. The heart examination showed expansile pulsation in the first intercostal space left, 3.5 cm. to the left of the sternum. The heart measured 14 cm. to the left. The sounds were loud; there was a systolic murmur over the precordium and a diastolic murmur heard best along the left border of the sternum. The blood pressure was 126 systolic and 45 diastolic in the left arm and 126 systolic and 54 diastolic in the right arm.

The sputum was negative for tubercle bacilli, occasionally it was blood tinged. The urine was negative. The Wassermann and Kahn tests were 4+. The patient's blood count showed 5,200,000 red blood cells, 90 per cent hemoglobin and 11,300 white blood cells.

Bronchography showed lipiodol blocked at the main left branchus. A diagnostic pneumothorax showed a pulsating shadow in the upper mediastinum, left. The left lung was collapsed and a small amount of fluid was seen at the base. On December 17, 1928, 350 cc. of pink opalescent fluid were aspirated from the left pleural cavity; 175 cc. of air were introduced, and it was seen that the mediastinum was still displaced. A few days later 150 cc. of blood-tinged fluid were aspirated from the left pleural cavity.

On December 26, 1928, paradoxical movement of the left diaphragm was noted. On this same day the patient had been coughing up blood, but was in good condition. During the night he was awakened from sleep by a massive hemorrhage in the mouth; he then lost consciousness in a few moments and died. An autopsy was performed disclosing a ruptured aneurysm of the aorta; the aneurysm had obstructed the left bronchus and had given rise to a massive atelectasis of the left lung.

Roentgen ray examination: (Fig. 4, a.) October 30, 1928: Unilateral opacity of the entire left side. Note the deviation of the trachea (left). No cardiac shadow is seen in the right side. The physical signs suggested fluid and aneurysm. Diagnosis: Massive collapse due to obstruction of left main bronchus. (Fig. 4, b.) December 10, 1928: Lipiodol shows complete obstruction of the main left bronchus. Note the visibility of the vertebrae as a result of the retraction of the left lung. Autopsy disclosed rupture of aneurysm of the aorta and massive atelectasis of left lung, probably from compression of left main bronchus.

Discussion. The history and physical findings of this case are quite suggestive of aneurysm. The various examinations suggested syphilis with aortic aneurysm but the unilateral opacity confused the picture. We thought that there was a tumor compressing the left main bronchus. Following the diagnostic pneumothorax, one could readily see from the Roentgen ray film that the aortic shadow was not much enlarged. Fluid from an atelectatic lung could be due to an intrabronchial tumor. There were no glands for biopsy. Bronchoscopy was considered as a diagnostic measure, but the danger of rupture of an aneurysm, if present, delayed the procedure. Postmortem showed an aneurysm of the arch of the aorta which had ruptured into the left main bronchus. The aneurysm itself was quite small, compressing the lumen of the bronchus almost to obliteration.

CASE 5.—*Tuberculosis of the Right Lung (Atelectasis).* T. W., a white man, aged 32 years, had symptoms of tuberculosis in the right lung with positive sputum. He had pneumothorax treatment elsewhere which was complicated later by massive pleural effusion. Repeated aspirations were done. On admission the physical signs were dullness throughout and bronchial breathing throughout the right chest, but no râles. His general condition was excellent.

Roentgen ray examination: (Fig. 5, a.) June 6, 1929: Lipiodol intro-

duced by the aspiration method shows the trachea and the main right bronchus dilated, the upper bronchus blocked, the middle partially and the lower one blocked completely. The left bronchial tree is normal. There is some oil in the stomach. Diagnosis: Pulmonary tuberculosis with fibrosis and partial atelectasis of the right lung. (Fig. 5, b.) September 6, 1929: Unilateral opacity of the right lung. Note the deviation of the trachea to the right. Below the right clavicle there is a crescentic-like area of rarefaction. The right diaphragm is not visible. The left lung shows compensatory air content. The cardiac shadow is retracted to the right. Impression: Pulmonary tuberculosis with fibrosis of the lung.

Discussion. As the Roentgen ray film shows a unilateral density the state of the bronchial tree is not apparent. By the introduction of the iodized oil its true condition was demonstrated. A diagnostic chest puncture was made to rule out the presence of fluid.

This case demonstrates the value of iodized oil in analyzing the condition of the bronchial tree.

NOTE.—The iodized oil was introduced by the aspiration method without the use of a local anesthetic. No reaction followed.

CASE 6.—*Empyema, Right Pleural Cavity.* L. F., a white boy, aged 15 years, was admitted to the Barnes Hospital, January 20, 1930, with a diagnosis of pneumonia. On December 9, 1929, he had an attack of pneumonia of the left lung which lasted 9 days. He seemed to be improving until 2 weeks before admission, when apparently pneumonia developed on the other side of his chest. At admission there were signs of consolidation and of fluid over the entire right chest, with rapid pulse (145), rapid respiration, cough, some expectoration of frothy fluid and cyanosis.

Roentgen ray examination: (Fig. 6, a.) January 20, 1930: Unilateral opacity of the entire right chest. Heart displaced to the left. No pulmonary markings noted. Signs of fluid. An aspiration showed a large amount of purulent fluid. (Fig. 6, b.) February 5, 1930: Film of patient after thoracostomy and drainage. The lung is partially expanded. Surgical pneumothorax (Dakin tubes in place). The heart has returned to its proper position. Diagnosis: Empyema, right pleura.

Aspirations of pus were made on January 21 and 22 followed by some relief. Because of the displaced heart and mediastinal contents, rapid pulse, fever, dyspnea and cyanosis, open drainage was delayed until January 24, when a thoracostomy with rib resection was performed by Dr. Graham. The cavity diminished in size rapidly and the patient was discharged on March 4, 1930.

Discussion. The history and physical signs and the Roentgen ray examination suggested fluid throughout the right chest, even before diagnostic puncture. The heart was displaced beyond the left mammary line; the trachea was not displaced and the diaphragm was not high. These findings show no evidence of massive collapse. Against pneumonia was the evidence of displaced mediastinum and the clinical history. The fluid aspirated proved to be thick pus. It was only after the aspiration of the pus that the true character of the disease was recognized.

Summary. The correct diagnosis of those conditions of the chest which produce unilateral opacities in the Roentgen ray films cannot be made from the Roentgen ray film alone. Six different cases have been presented in support of this view. The correlation of history and physical signs with the diagnostic procedures of bronchography and diagnostic pneumothorax are necessary.

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SUPERFICIAL THROMBOPHLEBITIS: A NEW CAUSE OF CHEST PAIN.

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DURING the past 3 years I have encountered 5 instances of pain in the chest due to an unusual cause. In an extensive review of the literature no mention is to be found of this entity as an etiologic agent of thoracic pain. It seems, therefore, worth while to report these cases as an aid in differential diagnosis.

Case Reports. CASE 1.—A colored male, aged 45 years, was seen on the wards of Garfield Memorial Hospital during the summer of 1927. This was a week following the onset of pain in the right chest, which was accentuated by deep breathing. He complained, too, of tenderness over the right lateral chest. On examination a tender sinuous cord, roughly 0.4 cm. in breadth, could be felt in the subcutaneous tissue. This cord extended from the right epigastrium upward and laterally to a point just outside the nipple where it was no longer palpable. It could be rolled under the fingers and was distinctly tender on palpation. The examination of the chest was otherwise normal. The further course is unknown.

CASE 2.—P. S. L., a colored female houseworker, aged 47 years, was seen in the outpatient department of Garfield Memorial Hospital on July 11, 1928. She complained of pain in the left chest of 3 weeks' duration. The pain was accentuated by deep breathing and by pressure. There had been no cough or other symptoms. No history of injury. One week previously a member of the staff had made a diagnosis of pleurisy and strapped the chest with adhesive. This gave no relief. On examination, after the strapping had been removed, a rounded cordlike structure could be felt running from the left epigastrium upward toward the axilla and passing just lateral to the left breast. The cord could be rolled under the fingers and was distinctly tender. The treatment consisted only of cold applications for relief of pain. The patient was again seen 6 months later

when there was no remaining abnormality. There had been no recurrence of pain.

CASE 3.—T. C. E., a white male Government employee, aged 50 years, was seen in my office on July 28, 1928, complaining of pain in the right chest just lateral to the nipple line. There was no relationship to deep breathing but the pain seemed to be distinctly increased on raising the right arm. Seven weeks before the present trouble began, a partial resection of the colon had been done because of acute diverticulitis. This was done through a left rectus incision but an enterostomy tube was left in the right lower quadrant for a few days postoperative. On examination of the chest there was localized tenderness in a line extending from the fourth interspace just lateral to the nipple downward and medially as far as the seventh interspace. A distinct cordlike structure about the size of a goose quill could be felt in the subcutaneous tissue. This cord could be rolled under the fingers and was quite tender. The temperature was normal. The postoperative course had been uneventful and there was no evidence of wound or skin infection. The pain and tenderness disappeared quickly without treatment. At present the cord cannot be felt and there are no residual symptoms.

CASE 4.—H. E. G., a white male office worker, aged 26 years, came into my office on February 6, 1929, complaining of pain in the right chest. He had had a healthy life and his past history threw no light on the present illness. Two weeks previously he noticed pain in the right chest near the costal margin in the region of the nipple line when he raised his arm. There also was tenderness on pressure in this region. A few days later the pain shifted upward to the sixth interspace, just lateral to the nipple line, and became more acute. There was an accentuation of the pain on deep breathing, coughing or sneezing. He applied local heat and massaged the area with counterirritants, but the pain persisted. Examination revealed a well-nourished, healthy looking young man with a temperature of 99.6° F. On the anterolateral portion of the right chest extending from the fifth interspace just lateral to the nipple line downward and medially to the epigastrium, a tender, rounded cord was palpated. This cord was about 0.3 cm. in breadth and could be rolled under the fingers. There was no tenderness except on direct pressure on the cord. When the arm was raised there was puckering of the subcutaneous tissue throughout the length of the structure described. It was not otherwise visible. No treatment was instituted except local cold applications for relief of pain. On February 14, 8 days later, the patient was seen again. The pain and tenderness in the original cord had disappeared, but it was firmer and more easily felt. Its course was longer, extending from 1.25 cm. above the costal margin to the level of the nipple. Its direction was toward the axilla. A similar tender sinuous structure was now noted running transversely from the original cord as far as the anterior axillary line at the level of the nipple. Physical examination otherwise revealed no abnormality. The urine was entirely normal, the leukocyte count was 9650; polymorphonuclear neutrophils, 75 per cent; large mononuclears, 2 per cent; transitionals, 2 per cent; lymphocytes, 21 per cent.

Two days later there was again a slight return of tenderness in the first vein involved, but less tenderness in the tributary. Ten days later all tenderness had disappeared from both veins and only the original cord could be palpated over a very short course. On June 28, 1929, 4 months after the first disturbance, the patient returned, complaining of exactly the same trouble but in the opposite chest. There was pain in the left chest on deep inspiration, on raising the left arm and distinct tenderness along the course of the vein. The vein involved was sinuous and markedly tender. It could be rolled under the fingers and extended about 12.5 cm. in length. Its course was vertical about 4 cm. lateral to the left nipple.

The temperature was 99.8° F. The leukocyte count was not unusual. Examination again was otherwise normal.

When seen 5 months later there was no palpable or visible abnormality on either side of the chest. The patient has remained well.

CASE 5.—Miss A. L., a white, unmarried Government employee, aged 46 years, came into the office on December 20, 1929. She complained of a sense of tightness in the lower left chest and upper epigastrium just lateral to the midline. This had developed 3 or 4 months previously and was associated with rather acute discomfort in the chest on deep inspiration. Soon after the onset the patient discovered a tender cord beneath the skin of the lower chest and upper epigastrium. Her previous history revealed nothing which threw light on the present illness. She had been thoroughly studied by me about a year before, because in a routine ophthalmologic examination an early retinal arteriosclerosis was noted. At that time, aside from the general atherosclerosis, albuminuria and cylindruria, no abnormalities were found. There was no enlargement of the heart and the kidney function was normal. The blood pressure was 120 systolic and 80 diastolic. On examination a distinctly tender subcutaneous cordlike structure about 0.3 cm. in diameter could be felt and rolled under the fingers. The cord extended from just above the umbilicus curving upward and outward almost to the left nipple. No treatment was advised. One month later the patient notified me that the sinuous structure had gradually extended downward to the umbilicus and then slowly disappeared. She is at present entirely well.

Comment. The obvious diagnosis in all these cases is a thrombophlebitis involving a superficial vein, which extends from the axilla downward and slightly medially toward the region of the umbilicus. It is most probably the thoraco-epigastric branch of the axillary vein. It is interesting that in each instance the pain is accentuated by deep breathing due undoubtedly to the stretching of the involved vein over the flaring costal border. In Case 2 the pain was so like that of fibrinous pleurisy that a member of the dispensary staff had previously strapped the chest. In no case was the cordlike vein visible and its presence was only recognized by gently passing the fingers over the skin of the chest. It is probable, therefore, that added attention to palpation in instances of chest pain will reveal more cases of superficial thrombophlebitis.

No etiology was ascertained for the disturbance reported except in Case 3. Here the thrombophlebitis was probably secondary to a low-grade infection of the abdominal incision. In none of the cases was there a history of syphilis or trauma. There was nothing present which could cause local stasis and there was no infection of the adjacent skin or subcutaneous tissue.

In 1922 Fiessinger and Mathieu¹ reported 3 cases of thrombophlebitis of the thoraco-abdominal wall following grippe-like infections. Two of their cases involved largely the abdominal portion of this same vein, the other was practically identical with the cases under discussion. Pain was not a feature in their report, though 1 patient did complain of slight epigastric discomfort. It is easily conceivable that painful involvement of the abdominal segment of

the vein might give trouble in the differential diagnosis of upper abdominal pain.

Summary. 1. Six instances of thrombophlebitis of a superficial chest vein are reported.

2. Chest pain was the predominant symptom.

3. Recovery without complication was the invariable outcome.

NOTE.—Since acceptance of this paper, a case report by Dr. George A. Williams, of Atlanta, describes in the *Journal of the American Medical Association*, 1 case with identical findings. This case was associated with dyspnea.

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THE SIGNIFICANCE OF THE COLLOIDAL GOLD REACTION AS A DIAGNOSTIC AND PROGNOSTIC AID IN NEUROSYPHILIS.*

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FROM the time Lange, in 1912, published his results on the colloidal gold reaction there has been a great deal written, particularly as to its value in differentiating the various forms of central nervous system syphilis. As is well known, considerable difference of opinion exists as to its specificity, especially in types other than general paresis. Information on the effect of antisyphilitic therapy on this test has for the most part been scanty, references being found either in a general discussion of the reaction or in the results with some type of treatment. Here again, the conclusions regarding the value of the changes found have been varied.

For these reasons, a study has been undertaken in this clinic to determine the correlation between the clinical diagnoses and the colloidal gold reactions in cases of untreated neurosyphilis and the type of change found in cases undergoing treatment. Most of the material for this study came from cases admitted to the department of dermatology and syphilology in the last 5 years. A few cases, however, were seen in the department of neurology. The clinical diagnosis was made only after the patients had been thoroughly studied.

The colloidal gold reaction was performed in the serological

* Studies and contributions of the Department of Dermatology and Syphilology of the University of Michigan Medical School, service of Dr. Udo J. Wile.

laboratory of the hospital. All colloidal gold solutions employed conformed to the following requirements: (1) Transparency of a brilliant salmon color with no trace of blue; (2) 5 cc. decolorized by 1.7 cc. of a 1 per cent sodium chlorid solution; (3) neutrality to alizarin red; (4) typical paretic curve with known paretic spinal fluid; (5) no change in color beyond a faint "red-blue" with a known normal spinal fluid. As a reducing agent in the preparation of the colloidal gold solution, formaldehyde was used up to September, 1929, and glucose since then.

The tests were carried out in the usual manner. The spinal fluid dilutions in 0.4 per cent sodium chlorid solution ranged in a series of 10 tubes from 1 to 10 to 1 to 5120. After adding the colloidal gold solution to each tube, as well as to a saline control, the mixture was incubated overnight at room temperature, when the final results were read. Complete decolorization of the fluid was noted as "5;" pale blue was read "4;" distinct blue as "3;" a color approaching lilac as "2;" and a bluish tint as "1." The "curves" given by the colloidal gold test with pathologic fluids are generally familiar to medical readers.

Relation of the Colloid Gold Reaction to Clinical Diagnosis. For this part of the study 700 cases were investigated. Of these there were 500 cases of neurosyphilis embracing 100 each respectively of early central nervous system involvement with primary or secondary syphilis, general paresis, tabes dorsalis, taboparesis, and diffuse cerebrospinal syphilis. This latter group includes vascular, meningo-vascular, and other types not falling into the other groups. As controls to this group 200 cases of syphilis without central nervous system involvement were used, namely, 100 cases of latent syphilis and 100 cases of hereditary syphilis. The diagnosis was made on all these cases from the clinical picture and other findings irrespective of the colloidal gold.

Lumbar punctures were performed as a routine measure on the patient's entrance to the clinic before any treatment was instituted. Care was taken in collecting specimens so that they did not come in contact with any substance which might give an untrue reaction. Any fluids containing blood have not been used as it has been shown by Black,¹ Kellert,² and others ^{3,4} that false reactions can be obtained.

For the sake of brevity and to do away with long columns of colloidal gold reactions, I have tabulated the curves, first, into the zones where the greatest color change takes place as suggested by Felton and Maxcy⁵ and, second, by the maximum intensity of this color change in one or more tubes. For example, a curve of this nature 0012332100 would be placed in Zone II, opposite 3, in the column showing the degree of color change. This is somewhat similar to the method that Larkin and Cornwell⁶ employed, except that they did not divide their curves into zones.

TABLE I.—SPINAL FLUIDS OF 700 CASES OF VARIOUS TYPES OF SYPHILIS SHOWING ZONE OF COLLOIDAL GOLD REACTION AND MAXIMUM COLOR CHANGE.

Reaction Zone I = greatest precipitation in first tubes containing higher concentration of spinal fluid; i. e., 55[54]32[10]00.
 Reaction Zone II = greatest precipitation in middle tubes containing moderate concentration of spinal fluid; i. e., 00[12]32[10]00.

	No. of cases.	ZONE I. Numbers showing maximum color change.					ZONE II. Numbers showing maximum color change.					Negative colloidal gold reaction.
		Numbers showing maximum color change.					Numbers showing maximum color change.					
		5.	4.	3.	2.	1.	5.	4.	3.	2.	1.	
Early involvement of C. N. S. with active primary or secondary syphilis	100	5	3	5	3	6	..	3	24	22	19	10
General paresis	100	65	17	2	1	1	1	4	4	2	3	
Tabes dorsalis	100	6	4	1	13	34	20	18	4
Taboparesis	100	32	13	4	1	1	..	4	11	16	14	4
Diffuse cerebrospinal syphilis	100	5	8	2	1	2	..	10	25	20	26	1
Controls
Latent syphilis	100	1	5	4	10	44	36
Hereditary syphilis with no evidence of neurosyphilis	100	1	..	1	2	7	39	50

Latent and Hereditary Syphilis. As a control to the group of cases showing neurosyphilis, we have used 100 cases of syphilis which show no evidence of cerebrospinal syphilis or active visceral involvement, and also 100 cases of hereditary syphilis with no clinical central nervous system manifestations.

In the group of latent cases (Table 1), 36 were entirely negative while 49 showed a maximum color change of "1," which falls well within normal limits. Eleven cases had a color change of "2." Greenfield and Carmichael⁷ also consider these slight reactions in normal limits. None of these cases had any suggestive evidence of cerebrospinal involvement on examination and their spinal fluids were otherwise entirely negative. Four cases of this group had a color change of "3." One of these patients had slightly hyperactive reflexes and another had slight inequality of the pupils. Both of these cases showed no further evidence of central nervous system involvement on subsequent examinations. Outside of this change in gold sol their spinal fluids were negative. The other 2 cases presented no abnormality on examination and their spinal fluid was otherwise negative.

Larkin and Cornwell⁶ found in a group of latent syphilitics some cases having color changes as marked as "4." They⁸ also found in epileptic patients 8 per cent with curves of "3" or higher. Miller,⁹ Cockrill,¹⁰ and Miller and Levy¹¹ all showed somewhat the same changes in similar groups. Warwick and Nixon¹² conclude that patients without syphilitic involvement of central nervous system give no colloidal gold curve, but one of their cases shows a curve of "3" and another one of "4."

In the congenital group 97 of these cases are within the usual normal range of reaction. However, here again one sees a few cases which have definite colloidal gold changes without any other confirmatory signs of nervous system involvement. The one case (Table 1) showing a precipitation of "4" had a syphilitic osteomyelitis of the frontal bones of the skull, but the neurologic examination was negative as well as the other spinal fluid findings.

In regard to these 2 groups of cases, the normal reaction could be considered to be "2" or less, but it should be kept in mind that from 3 to 4 per cent will show marked changes and the clinical and other laboratory examinations will be entirely negative.

Central Nervous System Involvement With Primary or Secondary Syphilis. All of the cases in this group at the time of the lumbar puncture showed active syphilis either in the primary or secondary stage. Also, most of them gave evidence clinically of some cerebrospinal involvement either by symptom, such as headache, dizziness or general malaise, or from examination, having either leukoderma colli, essential alopecia, hyperactive reflexes, or other signs of meningeal irritation. In many of the cases the cell count was extremely high, 200 to 300. The types of curves varied considerably, from

10 which were negative to 8 definitely of the so-called paretic type. Five more cases were also rather high in Zone I, having a color change of "3." This finding is most interesting when one considers that 13 per cent of these early cases gave colloidal gold curves usually associated with general paresis. A much larger group showed the rather high middle zone curve which is associated with diffuse involvement. There were 49 cases of this class.

Stokes¹³ has found the paretic curve rarely in this type of case, but further states that it does not necessarily mean a paretic outcome. The outcome of these cases in this series will be further discussed under therapy. Solomon¹⁴ also has found that most of the curves are weak, but that the stronger reactions are occasionally met with. Moore¹⁵ in a very extensive article on early nervous system involvement in syphilis found a rather large group with a paretic type of curve. Fordyce¹⁶ also states that it is frequently seen.

General Paresis. Since the introduction of the colloidal gold test it has been thought that a strong precipitation in the first tubes was nearly a uniform diagnostic finding in general paresis. Our results tend to bear this out for the most part in that 65 of the cases had a Zone I change with a maximum color change of "5," while 19 others presented the same type of curve but the maximum color change was of less intensity, "3" or "4." Nine cases gave slight changes which in view of the control series should be regarded as normal. Curves showing strong middle zone reaction also occurred in 9 cases.

In the latter 2 types most of the cases are early, with only slight mental deterioration. Under treatment only 2 later showed the typical high first zone reaction.

The incidence of "paretic" curves in paresis varies from 100 per cent found by Miller and Levy¹¹ to 84 per cent found by Rawlings.¹⁷ Many others have reported on this type of syphilis and most of their reports average about 90 per cent typical curves. Thompson¹⁸ in a large series, 639 cases, found 92.2 per cent high Zone I curves.

Differentiation of paresis into early and advanced types by Larkin and Cornwell⁸ showed about 98 per cent of the advanced types had the "paretic" curve, while only 66 per cent of the early form showed this reaction. Our series is somewhat lower than that usually reported and this may in part be accounted for by the fact that we see many patients whose symptoms are of short duration and not particularly marked. Likewise reports from psychiatric institutions where a good deal of this work has been done would tend to be higher.

Tabes Dorsalis. The reactions found in this group are of much less intensity than found in general paresis. Forty-two cases gave normal reactions, 4 of them being entirely negative, 18 showing only a precipitation of "1" and 20 showing a precipitation of "2." The rather high middle zone curves usually considered typical of tabes was found in 47 cases, while the "paretic" type was noted in

11 cases. Of this latter group 4 changed from a "paretic" curve to a "tabetic" curve later under treatment.

It is most important to note that in this type of involvement one finds such a large percentage (42) having normal response in the colloidal gold. Larkin and Cornwell⁶ in a small series of 22 cases had 50 per cent fall into this group. Greenfield and Carmichael⁷ in a much larger series also found a high per cent (40) with normal curves. On the other hand, especially by earlier authors, tabes was considered to give a rather uniform type of reaction; some, such as Lee and Hinton,¹⁹ reporting uniform high Zone II curves. As has been noted frequently before, this series presents also an appreciable number of "paretic" curves.

Taboparesis. One would expect to find the reactions of this group about midway between that of tabes and paresis, and such is the case. The number of high first zone curves are half the number that were found in general paresis, while there is marked increase of the number of weak reactions, 4 of the cases being entirely negative. There is a subsequent decrease of the strong middle zone reaction of the tabetic group.

Diffuse Cerebrospinal Syphilis. The reports on this type of nervous system involvement are varied, but they agree in the main that there is no characteristic reaction of the group, the middle zone type of reaction being met with most frequently. Nearly all showed some "paretic" curves. In the cases reported by Thompson¹⁸ 50 per cent showed a "paretic" curve. He concludes that colloidal gold is of no value in differentiating between cerebrospinal syphilis and paresis. At the other extreme, Vogel²⁰ showed in his cases of cerebrospinal syphilis that the intensity of the reaction was less than his group of tabetic fluids.

In this series half of the reactions are within normal limits, the others being more intense and falling either in the first or second zone. There were 15 cases of the high Zone I type so frequently seen in paresis.

Discussion. From Table 1 one readily sees that no one type of neurosyphilis presents a constant colloidal gold curve, but that a wide variation occurs in each group. In the cases of general paresis the finding of a similar type of reaction is most frequent. Here 84 per cent of the cases gave a strong precipitation in the first zone, while the other 16 per cent gave weaker reactions and most of these in the second zone. The curves occurring in the other types of involvement showed nothing characteristic except that in a general way the tabetic and diffuse cerebrospinal cases tended to react in the second zone with a rather slight amount of precipitation. A diagnosis therefore from the colloidal gold alone is impossible. In general paresis where a characteristic curve occurs frequently, it may well be considered a confirmatory finding but one should not rule out this diagnosis if the curve is not typical. On the other hand,

the finding of strong precipitation in the first group of tubes does not necessarily imply paresis, as all of the groups of neurosyphilis showed some cases in which this was present. The taboparetics have the highest per cent of this type of curve, that of 32.

Because of this variance of the colloidal gold reaction in each type of syphilis, the use of the reaction as an aid to differentiating one type from another should be used with reservation and more reliance placed on the clinical picture.

The occurrence of a slight or even a fairly strong colloidal gold reaction in a patient who shows no clinical evidence of central nervous system involvement and in whom the spinal fluid remains negative except for this colloidal gold reaction on subsequent examination, should be regarded as normal for that individual. As has been shown in Table 1, 57 per cent of the cases without central nervous system involvement show precipitation in some tubes varying from "1" to as high as "4."

The Effect of Antisyphilitic Therapy on the Colloidal Gold Reaction. The changes in colloidal gold reaction were studied in 413 cases under treatment for neurosyphilis. Of this number, 127 were treated by intradural therapy, 138 by tryparsamide, and 148 by malaria. The number of spinal punctures done on each individual patient varied considerably. Some of the malarial patients had but 2 spinal punctures, 1 before and 1 after therapy, while some of the patients who received tryparsamide had as high as 29 punctures. The average number of spinal tests in the patients receiving intradural therapy or tryparsamide was between 7 and 10. After malaria therapy the average was 2 to 3. The reason for this small number is because many of the patients failed to return for check up examinations.

It is impossible to record all the changes noted in each individual case. The variation of one reaction to the next may be only a slight change in intensity, or may be marked with also a change in the zone of maximum reaction. Nearly all of the cases showed some differences from time to time. In attempting to determine the extent and number of the major fluctuations occurring in an individual case undergoing treatment, we have recorded the number of times that the colloidal gold shifts from one zone to the other. Also, we have recorded the difference in the maximum color reaction from the time treatment was started until it was stopped. For example, a patient starting treatment had a gold sol of 0012332110. At the end of treatment the gold sol was 0001110000. The difference of maximum color intensity in this case would be a decrease of 2. Not infrequently after therapy the gold sol would be more marked in its reaction and this is recorded as an increase in intensity. The amount of increase depends on the difference between the original test and the last one taken. No record has been made of the differences of intensity occurring after each individual treatment.

The cases receiving a certain type of therapy have been grouped according to their clinical diagnosis.

All of the cases reported have been treated by the department of dermatology and syphilology.

Intradural Therapy. One hundred and twenty-seven cases were treated by this method. Of this group 14 cases were early nervous system involvement having active syphilis at the time of the original examination. In addition there were 25 cases of general paresis, 24 cases of tabes dorsalis, 24 cases of taboparesis, and 40 cases of late diffuse cerebrospinal syphilis.

The method of intraspinal therapy is that originally described by Wile²¹ in which arsphenamin (0.00025 gm.) is mixed directly with the spinal fluid and immediately reinjected. The patients receive these treatments weekly for a period of 4 weeks and then are given a rest period of 3 months. At the end of that time they receive another course, usually of two treatments. These were carried on as long as they were thought of value to the patient. Along with the intradural therapy, intravenous injections are given, also heavy metals, either bismuth injections or mercury inunctions.

Zone Change. As shown in Table 2, about half the cases in each group presented the same type of curve at the end of treatment as they had at the beginning. In the 14 cases of early nervous system involvement, 10 showed no zone shift and the remaining 4 shifted only once. All of these latter 4 cases had definite paretic curves to start with and later showed a shift from the first zone to the second and a marked decrease in the amount of precipitation in the individual tubes. This change occurred after only 3 to 4 treatments. There was 1 case which was originally of Zone I type and remained so at the end of 3 intradural treatments and some intravenous therapy. He failed to return for subsequent therapy so that the eventual outcome could not be determined. Except for this case, all of the others that showed no zone change were of the Zone II type. This rapid change from a strongly paretic curve to one within normal limits has been observed by Fordyce¹⁶ in this type of case.

In tabes dorsalis, taboparesis and late diffuse cerebrospinal syphilis, a little over half the cases showed no zone change following intradural therapy (Table 2). Most of the cases that did have a change in zone reaction occurred only once or twice. However, the shift of one zone to another was noted 6 times in 1 case of tabes. The most frequent change in these cases was that of Zone I to the middle zone.

In general paresis which is usually considered the most constant of reactions, we found that less than half remained in the same zone in which they started. Here again there was tendency for the curves to become middle zone in type under therapy. This is not, however, a constant finding, some cases eventually shifting back to the original first zone type and remaining there at the cessation of treatment.

There is a considerable variance of opinion as to the persistence of paretic type of curve. Kaplan and McClelland²² noted that the curve was stationary under treatment and considered it in the nature of a "Wassermann-fast" condition. Hammers²³ and Green²⁴ also noted changes only in a small group of treated cases. Thompson,¹⁸ Swalm and Mann²⁵ on the other hand noted a definite tendency for the paretic type to become middle zone under therapy. Klerret² reported a case of taboparesis showing several shifts from one zone to another. Warwick²⁶ found only a few instances of zone change in her series, which is rather large. This article also contains an excellent review of the subject. Greenfield and Carmichael⁷ state that under treatment the colloidal gold stays constantly paretic in general paresis except that there are occasional changes to the luetic zone due to irritation from interspinal treatment. We have seen this shift from a paretic to a middle zone curve so frequently, and in many cases in which the latter curve becomes constant, that it is difficult to feel that it is all explained on an irritation basis.

TABLE 2.—INTRADURAL THERAPY IN 127 CASES OF NEUROSYPHILIS SHOWING THE FREQUENCY OF ZONE CHANGE IN THE COLLOIDAL GOLD REACTION.

	No. of cases.	Numbers representing frequency of zone change.						
		No change.	1.	2.	3.	4.	5.	6.
Early C. N. S. involvement with active syphilis	14	10	4					
General paresis	25	11	4	3	3	3	1	
Tables dorsalis	24	14	4	3	1	1	1	1
Taboparesis	24	15	5	3	1	
Diffuse cerebrospinal syphilis	40	24	6	4	3	1	2	

TABLE 3.—INTRADURAL THERAPY IN 127 CASES OF NEUROSYPHILIS SHOWING AMOUNT OF COLOR CHANGE IN THE COLLOIDAL GOLD REACTION.

	No. of cases.	Decrease in color. Numbers representing the amount of change.					Increase in color. Numbers representing the amount of change.					No color change.
		5.	4.	3.	2.	1.	5.	4.	3.	2.	1.	
Early C. N. S. involvement with active syphilis	14	1	5	5	2	..	1
General paresis	25	3	2	5	2	13
Tables dorsalis	24	..	1	3	6	7	2	2	3
Taboparesis	24	5	2	6	4	7
Diffuse cerebrospinal syphilis	40	1	6	14	1	1	4	13

Color Change. In the majority of cases a decrease in the intensity of the reaction was noted (Table 3). For the most part this was

slight, the difference of maximum color being only "1" or "2" after treatment. One case of tabes showed the largest decrease, that of "4." The change in color cannot be expected to be very great when one considers that most of the cases before therapy showed the strongest precipitation as being "3" or less. Therefore a decrease in color even if the gold sol became perfectly flat could only be 3, or in the case of an original maximum precipitation of "2" a decrease on only 2 is possible. One would then expect the most marked changes of color intensity to take place in the group of general paresis where many of the fluids give readings of "5." This, as noted in Table 3, is not the case. Half of the cases showed no change at the end of therapy and this group corresponds nearly exactly with the group found in Table 2, which showed no zone shift.

The cerebrospinal group had one-third of the cases remaining stationary as to intensity of color reaction after treatment.

Each type of neurosyphilis presented a few cases in which there was a stronger color reaction following treatment than the patient presented originally. None of these increases in color could be interpreted as provocative in nature as described by Warwick and Nixon.¹²

In the treatment of 5 cases intraspinously, Vogel²⁰ notes a progressive flattening which was in accord with the clinical improvement and believes this to be a more objective indicator of improvement than the decrease in cells and globulin reaction. Many others have also noted the decrease in intensity of the color reaction. Warwick²⁶ concludes that there is a tendency for the reaction to decrease under antisiphilitic treatment, but she notes also that an increase can occur similar to what we have found in this series.

Tryparsamide Therapy. One hundred and thirty-eight cases were studied which received this type of treatment. Thirty-four of these were tabes, 35 general paresis, 19 taboparesis, and 50 late diffuse cerebrospinal syphilitics. The patients were treated in the following manner. Weekly injections of tryparsamide were given intravenously for six weeks and then there was a rest period of 2 months and the course was again repeated. Some of the patients received as high as 50 injections over a period of $2\frac{1}{2}$ to 3 years. Along with the tryparsamide either mercury inunctions or intramuscular injections of bismuth salicylate were given. During the first course of treatment spinal drainages were performed after each injection. In the subsequent courses drainage was done only after every other injection.

Tables 4 and 5 dealing with tryparsamide therapy have been made up in the fashion as that described above and used in showing the changes under intradural treatment. Namely, the numbers of zone shifts have been recorded and also the difference in maximum color intensity before and after treatment.

TABLE 4.—TRYPARSAMIDE THERAPY IN 138 CASES OF NEUROSYPHILIS SHOWING THE FREQUENCY OF ZONE CHANGE IN THE COLLOIDAL GOLD REACTION.

THE FREQUENCY OF ZONE CHANGE.													
	No. of cases.	Numbers representing the frequency of zone change.											
		No change.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
General paresis .	35	11	9	3	3	3	3	1	2		
Tabes dorsalis .	34	18	7	5	2	1	..	1		
Taboparesis .	19	12	4	1	..	2							
Diffuse cerebro-spinal syphilis	50	24	7	6	4	4	..	2	1	1	1

TABLE 5.—TRYPARSAMIDE THERAPY IN 138 CASES OF NEUROSYPHILIS SHOWING AMOUNT OF COLOR CHANGE IN THE COLLOIDAL GOLD REACTION.

	No. of cases.	Decrease in color. Numbers representing the amount of change.					Increase in color. Numbers representing the amount of change.					No color change.
		5.	4.	3.	2.	1.	5.	4.	3.	2.	1.	
General paresis . . .	35	..	3	2	8	8	2	12
Tabes dorsalis . . .	34	3	5	13	..	1	1	1	4	6
Taboparesis . . .	19	1	1	5	1	5	6
Diffuse cerebrospinal syphilis	50	4	5	11	1	8	21

Zone Change. The shift from one zone to another was frequently met with in all types of cases in this series. However, the cases of general paresis were the only ones in which more than half showed some shift. In this group only about one-third remained in the same zone in which the maximum reaction occurred before treatment. There were a large number which changed from a "paretic" to a middle zone reaction and remained that way during treatment. Two cases shifted from one zone to the other 9 times. The taboparetic group was the most stable during treatment, 12 of the 19 cases remaining unchanged, and the highest number of shifts noted in this group was four.

The tabetic and cerebrospinal cases presented similar pictures, about half of the cases in both groups remaining stationary. One of the cerebrospinal cases oscillated back and forth from one zone to the other 11 times. This case before treatment showed a Zone II reaction and finally at the end of treatment presented a similar type of curve.

Color Change. The maximum color change was decreased or increased in a majority of all the groups of cases, as shown in Table 5. The cerebrospinal group showed less change than the others, 21 cases out of 50 remaining unchanged. All but 6 of the 34 tabetic cases showed either a decrease or increase in the intensity of the

reaction. About one-third of the paretic and cerebrospinal cases remained unchanged.

The group of general paresis that showed no color change corresponds nearly exactly to the group which had no zone change. These cases were of the typical "paretic" type (marked precipitation in the first part of the curve). A similar group was found in the cases treated by intradural therapy.

As in the cases receiving intradural therapy the decreases in color was for the most part slight. The most marked change in this respect was seen in 3 cases of paresis in which the decrease was that of "4."

There was a stronger reaction at the end of treatment in a considerable number of each group. Six of the taboparetics or one-third of the total number showed an increase, while only 2 cases of paresis had more intense reactions at the end of therapy.

Since the advent of tryparsamide there has been considerable difference of opinion as to its effect on the spinal fluid as well as its general therapeutic value in neurosyphilis. Lorenz, Loevenhart, Blechwen and Hodges²⁷ reported marked improvement in colloidal gold under this type of therapy. Many of the initial "paretic" curves became luetic in type. A relatively large number became entirely negative. Similar improvement was noted by Moore, Robinson and Lyman²⁸ and Moore, Robinson and Keidel.²⁹ Flattening out of the "paretic" curve was also observed by Carr.³⁰ Fong³¹ in his series of cases found none that became negative but the majority showed some reduction in intensity.

On the other hand, Ebaugh and Dickson³² found the serologic changes meager and transitory. Wile and Wieder³³ occasionally noted certain minor changes, but the "paretic" curve remained so after therapy. Only slight, indefinite responses were also found by Solomon and Viets,³⁴ Banford,³⁵ and Foster.³⁶

Malaria Therapy. This group includes 148 cases of neurosyphilis which were treated by malaria. Of these 4 had early nervous system involvement with active primary or secondary syphilis, 73 general paresis, 13 tabes dorsalis, 32 taboparesis and 26 with late diffuse cerebrospinal syphilis. All of these cases were punctured immediately before inoculation with the plasmodium and again as soon after the chills had been stopped as was practical. A number of the patients failed to return for a check up so that there is only a record of two punctures in some cases. The others returned at intervals of 3 months for subsequent check-up examinations and lumbar punctures. In the interim some of them received heavy metals, either mercury or bismuth. The zone changes and the differences of the maximum color reaction have been tabulated (Tables 6 and 7) similar to the cases that received intradural and tryparsamide therapy. All cases have been used, those receiving only two punctures and those having more than that number.

TABLE 6.—MALARIA THERAPY IN 148 CASES OF NEUROSYPHILIS SHOWING THE FREQUENCY OF ZONE CHANGE IN THE COLLOIDAL GOLD REACTION.

	Numbers representing the frequency of zone change.				
	No. of cases.	No change.	1.	2.	3.
Early involvement with active syphilis	4	4			
General paresis	73	41	25	4	3
Tabes dorsalis	13	9	4	1	
Taboparesis	32	18	10	3	1
Diffuse cerebrospinal syphilis	26	17	5	4	

TABLE 7.—MALARIA THERAPY IN 148 CASES OF NEUROSYPHILIS SHOWING AMOUNT OF COLOR CHANGE IN THE COLLOIDAL GOLD REACTION.

	No. of cases.	Decrease in color. Numbers representing the amount of change.					Increase in color. Numbers representing the amount of change.					No color change.
		5.	4.	3.	2.	1.	5.	4.	3.	2.	1.	
Early involvement with active syphilis	4	..	1	..	1	1	1
General paresis	73	1	1	4	18	11	5	33
Tabes dorsalis	13	2	5	6	1
Taboparesis	32	5	2	8	2	4	11
Diffuse cerebrospinal syphilis	26	1	7	7	3	8

Zone Change. The shift from one zone to another is less marked in the malarial-treated group than in the other forms of therapy. This may in part be accounted for by the fact that there are no long series of punctures, the most that one patient received being eight. Well over half of the cases in each type of neurosyphilis showed no zone change. In the cases with active syphilis all of them remained the same. Three of the cases had Zone I curves and the other a Zone II type.

Approximately two-thirds of the tabes and taboparetics stayed stationary. Of the cases showing a shift of zone none of them were very marked. Three cases of general paresis shifted 3 times and 1 case of taboparesis shifted once. O'Leary³⁷ found many cases of paretics in which there was a change to Zone II type of curve and also that this was more frequent in malaria than with the other types of therapy.

Color Change. The color change from the maximum intensity noted before treatment to that after treatment is striking. All but one of the tabes cases showed some change, while the others with

the exception of the paretics showed a difference in two-thirds to three-fourths of the cases. In the group of general paretics well over half had a decrease or increase after malaria.

The amount of decrease in the precipitation of the colloidal gold is more marked with this type of therapy than with the others. Two cases showed a reduction of "4," while one case of paresis changed from a maximum color reaction of "5" to "0." This is a more marked change than has been found in either of the other two types of treatment.

An increase of color reaction at the end of therapy was noted again in a small group.

The effect of malaria on the colloidal gold has been considered slight by Huston and Armstrong,³⁸ and Carr.³⁰ Ferraro and Fong³⁹ agree that it is more resistant than the Wassermann and other reactions, but they make the further observation that, while the colloidal gold changes only little at first, at the end of 3 years there is an improvement in about 85 per cent of paretics and a few in which they become negative.

Therapy by Spinal Drainages Only. A small group of patients who had received no antisyphilitic therapy were given a series of spinal drainages. These were performed 2 or 3 times a week for 2 weeks so that in all they received from 4 to 6 spinal punctures. This was done to determine what change would take place in the colloidal gold without any definite antisyphilitic treatment. This group is so small that the results cannot be conclusive but one finds some interesting changes. There was 1 case of general paresis which showed a Zone I reaction with a maximum precipitation of "5." This remained constant in a series of 5 drainages. In 1 case of tabes and 1 case of diffuse cerebrospinal syphilis the zone of reaction remained the same, but there were slight differences of maximum color change noted from one drainage to the other and also the number of tubes showing color changes varied. A case with active secondary lesions and an early central nervous system involvement showed only slight color changes. The most striking changes were noted in 2 cases of taboparesis. One of these started with a strong Zone I curve, which upon subsequent examination varied in intensity, and after the third lumbar puncture shifted to a Zone II curve with a maximum color change of "3." The other case first presented a Zone II type of curve, which on the next examination shifted to a strong Zone I reaction. The following 3 examinations revealed the same type of reaction. The fifth colloidal gold reaction was again identical with the original.

The fact that in this small series the patients having taboparesis showed the most marked change does not necessarily mean that it is characteristic of this type of involvement. Similar changes have been noted in other types of syphilis where repeated spinal punc-

tures have been done without treatment. However, in this series the changes noted in the other types of syphilis were slight.

In advanced cases of general paresis which have been committed to the University Psychopathic Hospital, the colloidal gold curves that have been taken at intervals without treatment tend to remain similar, but occasionally one finds a case in which there is a change both of zone of reaction and the amount of precipitation.

From this small series of cases it is obvious that the colloidal gold is by no means stable in its reaction and that it varies from time to time in an individual case which is not receiving any specific treatment. For the most part these changes are so slight as to be negligible but marked differences do occur, as was noted in the 2 cases of taboparesis.

Discussion. The changes in the colloidal gold reaction found after any type of antisyphilitic therapy present a confusing and inconclusive picture, as is noted from the tables showing the effect of treatment. Changes similar to those found with treatment may occur when only a series of spinal punctures are performed in the absence of all other therapy. This was noted particularly in 2 cases of taboparesis in which this was done. If one attempts to consider reduction or zone change of the colloidal gold as of prognostic significance, it should be done guardedly, realizing that marked changes can occur in a short time after the original examination without any intervening therapy. However, there is a tendency for Zone I curves to change to the middle zone in all types of treatment and for Zone II curves to remain so. This is not characteristic of any special kind of therapy but occurs frequently with all types.

In a general way one can say that under treatment there is a reduction in the maximum color intensity and that the amount of reduction is about the same in all types of therapy. Under malarial treatment it was a little more pronounced and here one finds the greatest decrease in any one individual case.

A very interesting finding with each type of treatment was that in a small group of cases there was an increase in maximum color change after treatment. Usually these increases were slight but one case of tabes dorsalis undergoing tryparsamide treatment showed an increase of "4." No definite explanation for this can be made out. Other workers have also found this increase after treatment and were unable to find any correlation between it and the clinical course of the patient. Apparently it has no significance as far as being an indication of retardation of improvement.

About a third of the cases receiving intradural and tryparsamide therapy presented the same color change at the end of therapy as they had at the beginning. The cases receiving malaria had a slightly larger group which did not change. This is somewhat surprising in that the most striking clinical improvements are

noted in this group and if the colloidal gold tended to follow the clinical course one would expect to find a decrease of precipitation paralleling their improvement.

Under each type of treatment there was a group of general paralytics which showed no change in zone of reaction and this group closely paralleled those which showed no color change. They remained fixed throughout treatment. Many of these cases did not improve under treatment but there were some, especially those treated with malaria, where clinical improvement occurred with no change in the colloidal gold. No other type of central nervous system involvement presented as large a group in which the curve stayed the same throughout treatment.

Conclusions. 1. Syphilitics without central nervous system involvement frequently show some changes in the colloidal gold curve. Usually the color change is not over "2" but stronger reactions do occur.

2. No one type of neurosyphilis presents a constant curve.

3. In general paresis a strong Zone I curve is found in a high percentage of cases.

4. A strong Zone I curve does not necessarily mean general paresis as it is found in all types of neurosyphilis.

5. A middle zone curve is not of diagnostic significance as it occurs frequently in all types of neurosyphilis.

6. No type of antisyphilitic therapy produced changes in the colloidal gold with enough uniformity to merit prognostic significance.

7. The zone of reaction changes frequently and this may occur many times under treatment.

8. Decrease of maximum color reaction is commonly met with following treatment, but increase of color reaction also occurs and these changes do not parallel the clinical course.

NOTE.—For the privilege of presenting this material and for many valuable suggestions, I am indebted to my chief, Dr. Udo J. Wile.

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CHRONIC ADULT IDIOPATHIC TETANY. REPORT OF A CASE.

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For clinical purposes tetany may be divided into the following types: (a) Infantile; (b) postoperative; (c) gastric; (d) hyperpneic, and (e) idiopathic.

The infantile type is the most common. It occurs most frequently during the so-called tetany months, March and April, the result chiefly of insufficient exposure to sunlight, and consequent vitamin D deficiency during the winter.

The postoperative type follows accidental removal, injury to, or occlusion of circulation to the parathyroids, usually occurring during extirpation of the thyroid gland.

The gastric and hyperpneic types are due to alkalosis.

Nothing can be said with certainty regarding the etiology of idiopathic tetany. All types of tetany except those due to alkalosis have one feature in common, a marked reduction in the blood serum calcium. In the tetany of alkalosis the blood serum calcium is normal. In adults, tetany is usually observed either as a post-operative condition, following thyroid surgery, or as the result of alkalosis from certain high obstructive lesions of the gastrointestinal tract.

In this communication, we are concerned chiefly with chronic idiopathic tetany, which, as its name implies, is a type of tetany for which no accepted cause has been established. The extreme rarity of this condition, particularly in adult males, has been emphasized by Liu,^{1,2} who cites a single case in a Chinese male, aged 46 years, which is almost a prototype of ours. A few cases have been reported in females. We have not accepted a great many recorded cases considered to be idiopathic tetany in adult males for reasons which appear to us to be adequate.

A critical analysis of the literature suggests that the infantile type of tetany occurs also in adults. It is our belief that many of these cases, reported as adult idiopathic tetany, conform in all essential respects, to the infantile type. For example: Falta and Meyers⁶ quote 528 cases of occupational idiopathic tetany in males, collected by von Frankl-Hochwart, of whom 223 were cobblers and

117 sailors. The symptoms of tetany in this group became manifested chiefly in March and April, with spontaneous remissions during the rest of the year. Obviously, their indoor occupation and seasonal incidence suggests that these cases are similar to the infantile type, due to vitamin D deficiency, from insufficient sunlight, diet poor in vitamin D, or both. They should not be called idiopathic tetany.

McCarrison⁷ has described a form of so-called epidemic tetany observed in natives of the Himalayas, in association with epidemic goiter. One would infer that tetany in these cases results from parathyroid deficiency which might be associated with epidemic goiter. However, where epidemic goiter is extremely prevalent, as in the Austrian Tyrol and Switzerland, associated tetany is excessively uncommon. Moreover, McCarrison states that when the Himalayans with epidemic tetany and goiter move to a different locality, spontaneous recovery from tetany occurs. It is therefore apparent that this so-called epidemic tetany of the Himalayans is not due to parathyroid deficiency associated with goiter, but to environmental factors, incident to diet and climate. It may likewise be concluded that these cases are similar to the infantile type and a secondary rather than an idiopathic tetany.

If, therefore, we are justified in our opinion, that these cases reported by von Frankl-Hochwart and McCarrison are not true idiopathic tetany in adult males because these and many others so reported have a demonstrable etiology, it is apparent that this cryptogenetic type is sufficiently unusual to recommend the report of the following case.

This patient, studied over a period of 4 years, had no seasonal remission of symptoms, no surgical operations, no symptoms or signs of any obstructive lesion of the gastrointestinal tract and no clinical or chemical evidences of alkalosis.

Case Report.—L. B., male, white, aged 38 years, first came under our observation in April, 1927. For the previous 6 months he had noted peculiar muscle spasms in the hands and arms with muscle cramps and undue fatigue in the legs, aggravated by any muscular effort. He described numerous attacks of sudden, momentary, complete loss of voice and difficulty in breathing. At such times before phonation became possible he noticed a loud crowing inspiratory stridor, and following this, speech was audible but very husky. He also described numbness and parasthesias of the hands, arms and legs, and noticed that frequently, when his arms were resting on a chair or on a desk, his hands would involuntarily go into spasm, with the thumbs drawn into the palms. He also described sudden attacks of transient diplopia which could be relieved by covering one eye, unaccompanied by either headache or vertigo. Parasthesias, muscle spasms and ocular symptoms occurred every day; loss of voice, many times a day. Apart from these unusual symptoms, there were no other complaints. Gastrointestinal symptoms were conspicuously absent and there had been no loss of weight. The patient exhibited no apprehension about his condition, regarding it in a detached, but interested sort of way. One year later diarrhea ensued with 5 or 6 liquid stools daily. A less pronounced diarrhea

has persisted until the present time, unaccompanied by anorexia, nausea or vomiting. At the time of his first examination he had attained his maximum weight (155 pounds) and this has remained practically constant.

The previous medical history was unimportant except for an attack of uncomplicated scarlet fever in childhood. There was no history of previous operations, on the neck or elsewhere, no history indicative of rickets or tetany in childhood, no unusual dietary habits and no history of acute or chronic gastrointestinal disease. No other members of the patient's family had or has similar symptoms. He conducted an advertising business, was outdoors a considerable part of each day, walked a great deal and played golf 3 or 4 afternoons a week in season.

Physical examination was essentially negative except for manifest evidences of tetany. Trousseau's and Chvostek's signs were positive, and the electrical reactions were those of tetany.

The following table tabulates the various therapeutic agents employed together with blood chemical studies before and during treatment.

THE VARIOUS THERAPEUTIC AGENTS EMPLOYED, WITH BLOOD CHEMICAL STUDIES, BEFORE AND DURING TREATMENT.

Date.	Treatment.	Blood serum.		Plasma.	
		Ca.	P.	NaCl.	CO ₂ †
April 25, 1927	None	5.8	5.4	...	74
February 15, 1928	Ca. lactate, gm. ij	6.1			
February 23, 1929	Ca. lactate, gm. vj	6.4	6.7	570	69
July 20, 1929	Ca. lactate, gm. vj; thyroid, gm. 0.2	6.4			
October 16, 1929	Ultraviolet radiation	7.1	6.8		
November 19, 1929	Viosterol, gtts. xx	6.8	5.9		
January 16, 1930	Viosterol, gtts. xxx	6.3	6.0	570	71
May 28, 1930	Parathormone 20 units (4 doses)	7.8	4.2		
November 10, 1930	Parathormone 20 units (6 doses)	8.3	5.0		
April 16, 1931	Parathyroid transplant, March 4, 1931	6.4	6.6		

In addition to these figures, isolated determinations were made of the blood pH, which was normal, of the basal metabolic rate which varied from -5 to -26 per cent, and of the gastric contents, the maximum figures of which were normal for free and total acidity.

Treatment with calcium lactate by mouth was begun in April, 1927, and except for brief intermissions, in order to evaluate the results of other therapy, has been continued to the present time. Two to 6 gm. per day have been administered. For a brief period of time this therapy was reinforced first by thyroid, gm. 0.2 daily and later by thyroxin gr. $\frac{1}{16}$ 3 times a day.

It was thought that the coincident low metabolic rate might have had some relationship to the parathyroid deficiency, because in hyperthyroidism there is an increase of calcium excretion while in myxedema it is decreased. However, Aub, Bauer, Heath and Ropes⁸ have shown that the level of serum calcium is no indication of the rate of calcium metabolism.

Our patient showed no evidence of myxedema. Whether the deficiency of parathyroid secretion is related to hypofunction of the thyroid cannot be proved, although it seems quite suggestive. Our data likewise showed

that thyroid feeding had no effect on the level of the serum calcium. Its influence on the calcium balance could not be studied because the patient was ambulatory.

In August, 1929, the patient stopped all oral medication and received 8 treatments of ultraviolet radiation, twice a week for 4 weeks. Following this, in October, 1929, viosterol was prescribed in doses of 20 drops daily; in December, this was increased to 30 and during February and March, 1930, the patient consumed 60 drops of viosterol each day. In May, 1930, he was given 20 units of parathormone daily for 4 days and in October, 1930, 20 units of parathormone was administered every other day for 6 days, at the end of which time, blood chemical studies were made.

In March, 1931, a normal parathyroid gland was removed by Dr. Charles H. Frazier from a patient with hyperparathyroidism and transplanted by Dr. Ulrich into the rectus muscle of our patient. The gland removed was identified as normal parathyroid tissue by frozen section of a small fragment before being transplanted.

Results of Treatment. The use of calcium lactate by mouth, produced immediate amelioration of symptoms with partial freedom from laryngismus and spasms of the extraocular muscles. Undue fatigability and cramps in the arms and legs have persisted. Abstinence from calcium for 48 hours was followed by immediate recurrence of all symptoms with their customary severity. Although the intravenous administration of large doses of calcium will temporarily relieve the tetany following thyroparathyroidectomy, evidence is lacking of its good effect in latent tetany of either the infantile or adult types. In 3 patients reported by Liu, 2 juveniles and 1 adult, there was neither symptomatic relief nor elevation of either the diffusible or nondiffusible blood serum calcium.

The addition of thyroid, later thyroxin, caused no demonstrable effect on his tetany but raised his metabolic rate. Ultraviolet radiation produced temporary relief of symptoms to the point where no calcium was required for 3 weeks after the course of treatment was completed. The symptoms then returned.

Viosterol, even in doses of 60 drops a day, was so completely without beneficial effect, that the patient was compelled to reinforce it with calcium, in order to remain in reasonable comfort.

Regarding viosterol, it may be said that strikingly favorable results have been reported by Hess and Lewis,⁹ and Gleich and Goodman¹⁰ in the treatment of infantile tetany by this drug, comparable to the results obtained by cod liver oil and ultraviolet light. Other workers have confirmed this opinion, so that it can confidently be stated that viosterol acts as a specific in infantile tetany.

The efficacy of viosterol in the treatment of other types of tetany is very questionable. In the experimental animal, using thyroparathyroidectomized dogs, Urechia and Popoviciu¹¹ and Greenwald and Gross¹² were unable to raise the blood serum calcium with viosterol. Hess and Lewis failed in monkeys, concluding from this that viosterol acted by stimulating the parathyroids.

Brougher,¹³ and Jones, Rapaport and Hodes¹⁴ on the other hand, report conspicuous elevations in blood serum calcium, and the latter observed an extraordinary hypercalcemia in one of his operated dogs, following the administration of viosterol.

Brougher,¹³ Hottinger¹⁵ and Stern¹⁶ have recorded favorable

results from the use of viosterol in human adult tetany. Brougher's most favorable result was in a patient with gastrointestinal tetany, which followed formidable resections of the small intestine.

He further reports its use in 4 cases where tetany followed subtotal lobectomy. *Symptomatic relief was obtained but no figures for blood serum calcium are cited in these cases.*

Liu failed utterly to relieve his case of idiopathic tetany with viosterol and there was no alteration in the blood serum calcium from its use.

We are unable to explain the symptomatic relief in our patient from the use of calcium. His improvement was not reflected in a conspicuous alteration of the blood serum calcium, although our studies do not include its fractionation into its diffusible and non-diffusible components. Perhaps an elevation of diffusible calcium could have been demonstrated but it could not have been conspicuous, as the total blood serum calcium was never raised above the tetany level, except upon the addition of parathormone.

Similarly, we do not know why ultraviolet radiation was symptomatically beneficial, especially since it apparently did not alter the fundamental state.

Uniformly good results ensue from the use of viosterol in infantile and juvenile tetany and in those forms of tetany in adults, erroneously called idiopathic, but more properly regarded as of the infantile type. In both the experimental animal and in adult humans, tetany induced by thyroparathyroidectomy has been relieved in some cases, in others it has failed completely. Its use in spontaneous idiopathic tetany failed in a single recorded case, that of Liu's, as it failed in ours.

It is reasonable to conclude that there may not only be a difference between thyroparathyroidectomized animals and man, but that there is even greater difference between the tetany in man occurring postoperatively and that which occurs spontaneously, as the idiopathic type. The absence of the thyroid in the postoperative type, and its presence in the idiopathic type may be very significant.

Of the various therapeutic measures employed, parathormone alone was capable of conspicuously elevating the blood serum calcium. During its use, and for a very short time thereafter, there was complete symptomatic relief, and complete though temporary abolition of the tetanic state.

Numerous attempts have been made to prevent or cure tetany in man by parathyroid transplantation. Borchers¹⁷ reports 5 cases of postoperative tetany so treated, all of which were observed for several years after operation. One patient had recurrence of tetany after $2\frac{1}{2}$ years—the remaining 4 were not completely cured but obtained very appreciable relief.

In our case, after 6 weeks, parathyroid transplant failed com-

pletely either to alter the fundamental tetanic state or to raise the serum calcium above the tetany level. A superficial wound infection at the site of the transplant probably killed the graft.

Summary and Conclusions. 1. Evidence is presented to indicate that the infantile type of tetany resulting from vitamin D deficiency may be observed in adults, from the same cause. Most of the cases of so-called chronic idiopathic tetany in adults reported in the literature belong to this infantile type, and should be so considered.

2. Chronic adult idiopathic tetany, especially in males, is an excessively rare disease. A patient is reported in whom this diagnosis is justified by the exclusion of all recognized causes for this condition.

3. We have had the opportunity over a period of 4 consecutive years to observe, clinically and by laboratory studies, the effects of various forms of therapy. Calcium lactate by mouth for some unknown reason produced symptomatic relief but failed completely to raise the serum calcium above the tetany level. Viosterol was totally ineffective. Thyroid feeding was followed by an elevation of the subnormal metabolic rate but had no effect either on the tetany or on the serum calcium. Parathormone, subcutaneously administered, produced complete relief of tetany and elevation of the serum calcium above the tetany level during the period of its use. Parathyroid transplant failed completely because the graft probably did not remain alive.

4. The specific effect of parathormone and the total failure of all other therapeutic agents to alter the fundamental state suggest that, in this case at least, chronic tetany resulted from hypoparathyroidism. There are no reports available of histologic studies, ante-mortem or postmortem, of the parathyroid glands in chronic adult idiopathic tetany, hence the pathologic anatomy of this disease is entirely unknown.

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REVIEWS.

INTRODUCTION TO THE HISTORY OF SCIENCE, VOL. II. From RABBI BEN EZRA to ROGER BACON (Parts I and II). By GEORGE SARTON, Associate in the History of Science, Carnegie Institution of Washington. Pp. 1251. Baltimore: The Williams & Wilkins Company, 1931. Price, \$12.00.

It is impossible to avoid superlatives in writing of this stupendous work, properly called "one of the major intellectual undertakings of the century." In Volume I, which appeared in 1927, the unusual nature and wide purpose of the work, begun in 1912, was explained. Each chapter devoted to a given period of varying length began with a summary of the main facts, constituting a short account of the development of science during that period. These with the introductory chapter were the only parts intended for continuous reading, the larger remainder being like a huge *catalogue raisonné* intended for reference and study. The ambitious purpose of the whole is to present and explain the whole development of science, that is, "systematized positive knowledge." The importance of such a task, especially when it concerns "the only human activity which is truly cumulative and progressive," will be readily granted. More doubt might be felt about the ability of any one individual to accomplish it, but few could foretell the astonishing industry and productivity of Dr. Sarton, who must truly have lived for his task and for but little else in the past 20 years.

Volume I covered from the dawn of Greek and Hebrew science through the time of Omar Khayyam. Egypt, Mesopotamia and other possible dawn spots were not included, both on account of the difficulties in the way of strict chronological arrangement and the author's professed lack of sufficient philological and archeological equipment. The second volume, covering the 12th and 13th centuries from Rabbi ben Ezra to Roger Bacon, has on account of its bulk been divided into 2 books but with continuous pagination and one index for both. Following an explanatory preface comes an introductory chapter of over 100 pages, which is a book in itself, presenting a survey of the thought of the 2 centuries on the 8 or 10 major branches of science. Next come 4 "books," one for each half-century, each divided into 13 or 14 chapters on a Survey of Science and Intellectual Progress, Religious and Philosophical and Cultural Backgrounds, the Translators, Education, the individual sciences and an appendix. As the 4 surveys are much the largest of these chapters (totaling another 275 pages), it results that more

than a third of Volume II is devoted to a connected line of thought and expression, not unrelieved by pleasing flights of fancy and dignified humor. In the mountains of scientific data, the names of individual scientists or scientific details can be easily found with the help of one large index of 109 pages. Thus Hippocrates appears, even in this volume, 37 times; Hunain b. Ishaq, 38; St. Thomas Aquinas, 51; Roger Bacon, 63 and Maimonidez, 70 times. As an example of the author's thoroughness, he has spent "much time and energy in the study of Arabic and Hebrew" in the past few years, to improve his knowledge of these languages and cultures and the results are apparent in the printed book. And yet, feeling his knowledge inadequate to allow him sufficient penetration of Jewish and Muslim minds, he is spending the present year in the East for further intensive study. This will shortly bear fruit in a Prolegomena to the history of science which will be even more complete than the Introduction of these 2 volumes. While the index of this volumes makes the work an excellent lexicon, and bibliographic details, occupying 15.7 per cent of the whole, make it an excellent bibliography of the science of the period, nevertheless the author rightly emphasizes its synthetic qualities and prefers to look upon it as "a scientific map with full indications of sources."

Just as Volume II, covering two centuries, is considerably larger than Volume I, covering 20, so the ever increasing stream of science will constantly add to difficulties of accomplishment. Nevertheless, the author rightly feels that he should be able so to indicate the path that other trained scholars will carry out the plan when he lays down the burden. His astonishing productivity leads us to hope that he may so far continue the work that the task of the others will be slight. In any case, what he has already accomplished ensures his fame as an historiographer. Every scientific library must possess this work and many individuals will choose to do so, especially as the aid of the Carnegie Institution has kept the price remarkably low. We have no adverse criticisms, and if we had, in the light of the above, would consider it presumptuous to offer them.

E. K.

LEZIONI DI MEDICINA BIOLOGICA. By C. MARTELLI. Pp. 548; illustrated. Naples: Edizioni Rinascenza Medica, 1930.

THIS is a collection from *Rinascenza Medica* of 66 articles by some 30 or 40 Latin authors, writing in Italian. There is a wide range of subjects, for instance, the first 11 are on medical philosophy, dermatology, tuberculosis, pathologic anatomy, surgery, acidosis, hematology and cancer (3). The approach is predominantly clinical. Attractions are the inexpensive but artistic binding, the inclusion of the author's portrait at the head of each article and a two to four

line summary beneath the title. Beyond making these articles somewhat more available, we fail to see much useful purpose in the publication. E. K.

A CLINICAL STUDY OF ADDISON'S DISEASE. By LEONARD G. ROWNTREE, M.D., and ALBERT M. SNELL, M.D., Division of Medicine, The Mayo Clinic and The Mayo Foundation. Pp. 317; 41 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, \$4.00.

THE recently discovered cortical hormone by Swingle and Pfiffner fortunately was available for use by the authors. This with the surprisingly large material available, and the skillful handling of the many aspects of the problem, make it an extremely valuable contribution. The 50 pages devoted to the history of the subject and to Addison's original cases give a background which should be emulated by more writers on clinical subjects. E. K.

BOOKS RECEIVED.

NEW BOOKS.

Electrotherapy and Light Therapy. By RICHARD KOVÁCS, M.D., Clinical Professor and Director of Physical Therapy, Polyclinic Medical School and Hospital, New York. Pp. 528; 211 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$6.50.

History of Medicine in the Province of Quebec. By MAUDE E. ABBOTT, B.A., M.D. Pp. 97; 41 illustrations. Montreal: Medical Museum, McGill University, 1931. Price, \$3.00.

Living the Liver Diet. By ELMER A. MINER, M.D., Independence, Kansas. With Introduction by WILLIAM P. MURPHY, M.D., Instructor in Medicine at the Harvard Medical School, Boston. Pp. 106; 3 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$1.50.

Growth in Private School Children. By HORACE GRAY, Stanford University Hospital, San Francisco, and J. G. AYRES, The Institute for Juvenile Research and Behavior Research Fund, Chicago. Pp. 282; illustrated with figures and tables. Chicago: University of Chicago Press, 1931. Price, \$3.50.

The Use of the Self. By F. MATTHIAS ALEXANDER, with an Introduction by PROFESSOR JOHN DEWEY. Pp. 143. New York: E. P. Dutton & Co., Inc., 1932. Price, \$2.00.

Female Sex Hormonology. By WILLIAM P. GRAVES, A.B., M.D., F.A.C.S., Professor of Gynecology at Harvard Medical School, Surgeon-in-Chief to the Free Hospital for Women and to the Parkway Hospital, Brookline. Pp. 131. Philadelphia: W. B. Saunders Company, 1931. Price, \$3.50.

Introduction to the History of Science, Vol. 2, From Rabbi ben Ezra to Roger Bacon (Parts 1 and 2). By GEORGE SARTON, Associate in the History of Science, Carnegie Institution of Washington. Pp. 1251. Baltimore: The Williams & Wilkins Company, 1931. Price, \$12.00. See review page 425.

- The Vitamins. Monograph of the Pickett-Thomson Research Laboratory, Vol. 1, September, 1931.* By ETHEL BROWNING, M.D., Liverpool, Assistant Pathologist to the Pickett-Thomson Research Laboratory, St. Paul's Hospital, London. Pp. 575; illustrated with 52 text and tables. London: Bailliere, Tindall & Cox; in America, Baltimore: The Williams & Wilkins Company, 1931.
- A Doctor of the 1870's and 80's.* By WILLIAM ALLEN PUSEY, Sometime President of the American Medical Association and of the American Dermatological Association. Pp. 153; illustrated. Springfield, Ill.: Charles C Thomas, 1932. Price, \$3.00.
- A Nonsurgical Consideration of Prostatic Enlargement.* By EDWIN W. HIRSCH, Associate in Urology, College of Medicine, University of Illinois; Urologist, Englewood Hospital, Chicago. Pp. 79; 6 illustrations. St. Paul, Minnesota: Bruce Publishing Company, 1931. Price, \$2.00.
- History of Medicine in the United States, Vols. 1 and 2.* By FRANCIS R. PACKARD, M.D., Editor, *Annals of Medical History*. Pp. 1323; 103 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, \$12.00.
- Imhotep to Harvey. Backgrounds of Medical History.* By C. N. B. CAMAC, M.D., Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University. Foreword by HENRY FAIRFIELD OSBORN, Sc.D., LL.D. Pp. 324; 2 illustrations. New York, Paul B. Hoeber, Inc. Price, \$3.75.
- Allergy and Applied Immunology.* By WARREN T. VAUGHAN, M.D., Richmond, Va. Pp. 359; 20 illustrations and numerous tables. St. Louis: The C. V. Mosby Company, 1931. Price, \$4.50.
- Manual for the Jewish Diabetic.* By WILLIAM S. COLLENS, B.S., M.D., Assistant Chief, Diabetic Clinic, United Israel Zion Hospital. Foreword by HENRY JOACHIM, M.D., Clinical Professor of Medicine, Long Island College of Medicine, Brooklyn. Pp. 138; 21 illustrations. New York: Bloch Publishing Company, 1931.
- Medicine in Virginia in the Eighteenth Century.* By WYNDHAM B. BLANTON. Pp. 449; illustrated. Richmond: Garret & Massie, Inc., 1931. Price, \$7.50.
- Nutrition Abstracts and Reviews, Vol. 1, Nos. 1 and 2, October, 1931.* Pp. 351. Aberdeen: The Aberdeen University Press, Ltd., 1931. Price, 13 shillings.
- Courts and Doctors.* By LLOYD PAUL STRYKER. Pp. 236. New York: The Macmillan Company, 1932. Price, \$2.00.
- A Radiological Study of the Para-nasal Sinuses and Mastoids.* By AMÉDÉE GRANGER, K.C.B., K.C.I., M.D., F.A.C.R., Professor of Radiology, Louisiana State University Medical Center; Director of the Department of Radiology, Louisiana State Charity Hospital, New Orleans. Pp. 186; 113 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$5.50.

NEW EDITIONS.

- Varicose Veins.* By H. O. MCPHEETERS, M.D. F.A.C.S., Director of the Varicose Vein and Ulcer Clinic, Minneapolis General Hospital. Pp. 235; 62 illustrations. Third edition revised and enlarged. Philadelphia: F. A. Davis Company, 1931. Price, \$4.00.

A new chapter has been added on "The Causes of Failure in the Injection Treatment of Varicose Veins," and the chapter on Elephantiasis has been expanded to include the "Elephantoid States Due to Lymphatic Obstruction."

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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AND

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Studies on the Relation Between Tumor Susceptibility and Heredity. V.. The Influence of Heredity Upon the Incidence of Lung Tumors in Mice.—CLARA J. LYNCH (*J. Exper. Med.*, 1931, 54, 747) writes that it is well known different constitutional types react in various ways to disease. Particularly interesting is the question of determining whether such types are inherited as the demonstration of inheritance of distinct types may aid in the diagnosis of conditions of nonbacterial origin. The experimental data that have been collected in the author's laboratory concern the incidence of lung tumors in mice are as follows: Strains in mice exist which differ markedly in regard to the incidence of spontaneous lung tumors in the several strains; these strains vary in liability to induced lung tumors and these differences are inherited. It is important to determine whether or not spontaneous tumors in the experiment involved in a cross between strains would parallel those yielded by induced tumors. The experimental work consisted of crossing a male mouse who came from the strain in which there was a high incidence of spontaneous lung tumors with several females from a low-tumor strain. The first generation was then backcrossed to individuals of the original strain. It was found in the backcross from strain D, the high tumor strain, that the incidence of tumor was extremely high, 130 in 204 mice, whereas the backcross from strain 1194, in a total of 218, the incidence was only 16 in the mice that were over 6 months. The more detailed observations cannot be recorded due to lack of space. Suffice it to say that the author shows that from all evidences there are undoubtedly among mice constitutional types which differ in incidence of tumors of the lungs and that these differences are inherited without any apparent influence of sex. She says also that the number of genetic factors involved has not been determined, and there is a possibility of there being such factors to affect tumor age.

SURGERY

UNDER THE CHARGE OF
T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Lesions of Isthmus (Pars Interarticularis) of Laminæ of Lumbar Vertebrae.—CHANDLER (*Surg., Gynec. and Obst.*, 1931, 53, 273) says that solution of bony continuity at the isthmus is a common lesion of the lower lumbar spine. The presence of such a defect can be determined clinically and by the proper interpretation of good roentgenograms of the lumbar spine. The stability and strength of the lumbosacral articulation is impaired by the presence of such defects. The developmental origin of such clefts has been assumed rather than proved. Further study of spines of the fetus and newborn is desirable. Fractures of the isthmus are frequently complicated by spondylolisthesis. Operation in selected cases will restore stability to the lumbosacral juncture.

Nonvenereal Prostatitis.—BRIGGS (*Urol. and Cutan. Rev.*, 1931, 35, 551) finds that the prostate is not ruled out as a focus of infection as often as it should be. Nonvenereal, nontuberculous prostatitis is insufficiently stressed in most of our standard textbooks. This review has led the author to believe that 18 to 20 per cent of all cases of prostatitis are of nonvenereal origin. A diagnosis of chronic prostatitis often requires several examinations, and in most cases the examination means much more than palpation. The symptoms are very variable. Treatment may or may not be satisfactory, but in most cases requires time and patience.

Carcinoma of the Thyroid Gland.—DUNHILL (*Brit. J. Surg.*, 1931, 19, 83) says that there are three types of cancer of the thyroid, scirrhus, papilliferous adenocarcinoma and malignant adenoma. In the thyroid gland epithelial proliferation is the characteristic response to stimulation. The proliferation may resolve spontaneously or under treatment. It may form a benign tumor or it may form a tumor which invades and disseminates. These stages merge into one another by insensible gradations. These histologic gradations cause difficulty in deciding just when a tumor has become malignant. Proliferation of thyroid epithelium may be papilliferous or follicular in type. Papilliferous adenocarcinoma may be an ultimate result of the former malignant adenoma of the latter type. A nodule in the thyroid should not be regarded as of no importance, and early changes in signs or symptoms associated with it should induce the practitioner to investigate the cause of these changes. Histologic examination should be made in every case of removal of thyroid tissue, and sections should be made in every case of removal of thyroid tissue, and sections should be taken from different areas. Advanced cases should not be regarded as hopeless when the condition of the patient justifies it, as much of the tumor should be removed as possible and then Roentgen ray treatment commenced. By this means comfort is given and life is sometimes prolonged to a surprising extent.

THERAPEUTICS

UNDER THE CHARGE OF
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Apomorphin in the Treatment of Paroxysmal Tachycardia.—VIKTOR WEISS (*Med. Klin.*, 1931, 27, 1608) reports most favorable results in the rapid control of paroxysmal tachycardia from the subcutaneous injection of 10 mg. of apomorphin. Favorable results were obtained in this one patient in five different attacks. The author discusses the use of apomorphin for this purpose emphasizing the fact that its potent emetic action is accompanied by powerful vagal stimulation. He cites one other report in the literature of a similar use of apomorphin. In closing he feels justified in recommending this agent both on the basis of its probable effectiveness and upon its safety. Attention is also directed to the fact that emesis induced by other methods has been proved frequently to abate attacks of paroxysmal tachycardia.

The Use of Sulphur in Peripheral Vascular Disease.—Marked benefit often follows the production of fever by the administration of non-specific proteins in patients with chronic peripheral vascular disease. This form of therapy, however, carries with it certain inherent dangers and disadvantages. In the intramuscular injection of sulphur, it also produces fever which is of much longer duration than that produced by most other methods and of which therapeutic use has been made in the treatment of tabes and paresis. WALLER and ALLEN (*Ann. Int. Med.*, 1931, 5, 478), therefore, tried the injection of sulphur in a series of patients suffering from thromboangiitis obliterans, arteriosclerotic occlusion in the extremities and patients with painful paresthesia. They found that a dose of from 1 to 3.5 cc. of a 2 per cent suspension of sulphur in olive oil was sufficient to produce a significant elevation of body temperature up to 2° C. above normal which generally occurred without severe chill, began gradually 6 or 7 hours after injection and lasted on the average of 2 days. It is seen from this latter figure that the pyrexia is of considerably greater duration than that produced by the proteins. A serious disadvantage, however, from these injections was found in the development of severe local pain at the site of injection. The therapeutic effects were quite as satisfactory as those following the intravenous use of proteins and sometimes considerably more satisfactory. Despite the disadvantages inherent in the severe local pain, the authors believe that the intramuscular injection of sulphur is particularly advantageous in elderly and greatly weakened patients because of its relative freedom from danger.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

The Blood Pressure in Boys and Girls Before and After Puberty.—RICHEY (*Am. J. Dis. Child.*, 1931, 42, 1281) as a result of this study found that the average blood pressures of children increase with age, except that the pressures of females tend to decrease after the 16th year. The forms of the pressure curves indicate that factors other than age are active in changing the slope and direction of the curves. Blood pressures of normal children of the same age vary within wide limits. There are also wide fluctuations of the pressures of any child, which may be explained, to some extent, in terms of known influencing factors. Normal blood pressure may be best described as a range. For larger groups of children, the size of the range does not appear to be influenced by sex, age or race. Significant differences exist between the pressures of the two sexes. The average systolic pressures of girls appear to be higher than those of boys for ages from 10 to 13. After 13 years the pressures of boys exceed those of girls, the differences increasing with age. The average diastolic pressures of girls and boys vary only within the limits of unreliability, but from 11 to 16 years the consistently higher absolute values for girls suggest real differences. The average pulse pressures of boys exceed those of girls after the thirteenth birthday, the difference increasing with age. Systolic, diastolic and pulse pressures are intercorrelated at all ages. The correlation coefficients expressing the relation between systolic and diastolic pressures and between systolic and pulse pressures are positive. The correlations between diastolic and pulse pressures are negative at all ages. These relationships have been interpreted to indicate that persons who have systolic pressures above average tend to have both diastolic and pulse pressures above the average, and according to Stocks those with diastolic pressures above average will tend to have pulse pressures below average but not by the same amount, so that the total or systolic pressures will tend to be above the average also. The negative correlations between diastolic and pulse pressures indicate that the higher the diastolic pressure, the less additional force is necessary to maintain circulation. The coefficients of correlation for systolic and diastolic pressures decrease with age, while those for systolic and pulse pressures increase. The relation between systolic and diastolic pressure changes as the higher levels that accompany increased age are attained. Systolic pressure and to a less extent, diastolic pressure are related to physical development. Systolic pressure is correlated with physical development independent of age. The correlation between height and systolic pressure disappears when weight is held constant. The differences of children as to precocity of sex maturation are reflected in the behavior of the blood pressure. Children different as to the precocity of maturing, are different as to anatomic and physiologic development at all ages before the onset of

puberty and, in some ways, for a number of years thereafter. Differences of the blood pressures of children of any given age are probably as pronounced as those in growth in general. In spite of the correlation between pressure and variables of growth, the physical superiority of children who mature early is not in itself sufficient to account for the behavior of the blood pressure.

Vaccine Treatment of Asthma in Childhood.—MITCHELL and COOPER (*Arch. Ped.*, 1931, 48, 751) comment that it is impossible to draw conclusions from such a report as this, but that their results and a review of the literature seem to indicate that a certain number of children, whose asthmatic attacks are associated with upper respiratory tract infections, are decidedly benefited by the use of vaccines, and in some attacks, which have previously been frequent and severe, cease for months or years after such treatment. Vaccines are helpful sometimes when other methods of treatment have failed. It is not clear whether the vaccine treatment acts by specific desensitization to microorganisms which the patient harbors in his nose and throat and which may be causative of the asthmatic attacks, or whether the mechanism is simply one of nonspecific protein therapy. In their work they have employed vaccines made from those microorganisms obtained from the patient's nose and throat, to which he was sensitive by skin test. It may be necessary to repeat the treatment with freshly prepared vaccines after a period of several months.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Dermatitis Venenata Due to Shoe Leather.—LEWIS (*Arch. Derm. and Syph.*, 1931, 24, 597) adds another cause to the already overburdened list of agents capable in susceptible subjects of provoking a contact dermatitis; confirming a similar observation by Bloch. The report is timely; however, inasmuch as the present tendency is to consider all inflammatory dermatoses of the feet to be of fungous origin. The 2 patients reported by the author had a dermatitis of the feet which was only relieved by finding a positive patch test with the offending shoe leather and removal of the cause.

Argyll-Robertson Pupils, True and False.—ADIE (*British Med. J.*, 1931, 136, 3681) introduces his subject by the apparently contradictory statement that the true Argyll-Robertson phenomenon is an infallible sign of syphilis yet pupils that react on accommodation but not to

light (the usual definition of an Argyll-Robertson pupil) are met with in some 20 odd conditions unrelated to syphilis. For a definition, the author reverts to the original paper of Argyll-Robertson in 1869 who described "4 cases of spinal miosis" in which, although the retina was quite sensitive and the pupils contracted at once on accommodation for near objects, there was no response to light and that only slow and partial dilatation occurred on the application of a strong atropine solution. The writer then proceeds to analyze this definition by stating that the typical A. R. pupil is small, not exceeding $2\frac{1}{2}$ mm. in diameter. Typically the A. R. pupil contracts at once and fully, often excessively, on convergence. Thereafter it dilates again promptly. Furthermore, the pupil in question remains the same size indefinitely regardless of the amount of light that enters it; false A. R. pupils often vary in size or dilate when shaded. The author defines the Argyll-Robertson pupil by the statement "small pupils, constant in size, unaltered by light or shade, contracting promptly and fully on convergence, dilating again promptly when the effort to converge is relaxed, and dilating slow and imperfectly to mydriatics. The pupils may be irregular or unequal; the lids may droop or be retracted." The author believes the term "fixed pupil" is an unfortunate one and should be reserved for pupils that react neither to light, direct or consensual, nor on convergence. Even such pupils often react on forcible closure of the lids. Syphilis is merely one of many causes of partially fixed pupils. In partial or recovering lesions of the third nerve, most often traumatic, the pseudo-Argyll-Robertson pupil of Axenfelt may be observed. The chief clinical features are: the condition is often unilateral; pupils vary in size from time to time; pupils never miotic; the reaction to light, though absent to ordinary tests, is not really abolished; the pupil dilates in the dark; the reaction on convergence is peculiar; accommodation, though normal in range, is sometimes slow; and prompt and full dilatation occurs with mydriatics.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Menorrhagia Treated by Pituitary Hormone.—A most interesting report by NOVAK and HURD (*Am. J. Obst. and Gynec.*, 1931, 22, 501) deals with the treatment of 51 cases of functional uterine hemorrhage by an anterior pituitary luteinizing substance derived from the urine of pregnant women. In 44 of these the treatment was successful in checking the bleeding even though some of the patients were treated with preparations of somewhat uncertain luteinizing potency. Previous efforts at the organotherapy of this condition have been unsuccessful.

Radiotherapy is very undesirable in young women, so that, because of the frequent intractability of functional hemorrhage, many patients have to submit to repeated curettage. The characteristic ovarian finding in these cases is an absence of corpora lutea. The administration of progestin, if this were available, would be a rational plan of treatment. Progestin, the hormone from the corpus luteum of the ovary, is not yet available for human administration, and its effect would be purely substitutional, as it has no effect on the ovaries. The administration of the luteinizing hormone of the anterior pituitary (prolan B) can be expected to be more fundamental in its effects. This substance has been shown by laboratory studies to produce striking luteinization in the ovaries, and the secretion of the lutein cells is progestin, the element lacking in functional uterine hemorrhage. The hormone can be obtained from the urine of pregnant women, although its extraction is as yet somewhat difficult. In 14 of the 51 cases in this series the bleeding ceased after a single injection, and in 12 after two injections. A large proportion of these cases were of the intractable and recurrent type, many having had from one to four or more curettements. In regard to the method of preparation of the hormone used in this work, it may be stated that the urine from pregnant women is concentrated and subjected to precipitation with water-soluble organic solvents, such as alcohol or acetone, thereby removing a large amount of inert material. Though both prolan A and prolan B are present in the resultant material, the dominant action is that of the luteinizing hormone. The rapidity of the effect in many cases makes it seem certain that the immediate effect is not brought about through the production of lutein tissue and progestin by the ovary. They believe that this immediate effect is exerted upon the still unknown bleeding factor which is the immediate cause of the bleeding in functional hemorrhage and which is influenced by far smaller dosage than would be required to produce histologic changes in the ovary. Their experience has convinced them of the value of this treatment in functional hemorrhages and of its even greater future possibilities.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Intraocular Blastomycosis.—SCHWARTZ (*Arch. Ophthalm.*, 1931, 5, 581) reports a case of metastatic iritis in a patient, aged 38 years, with systemic blastomycosis, in whom the primary lesion was in the lung. coincident with the onset of the iritis a number of superficial abscesses developed. The patient died within about two months. When the

eye was first examined, in addition to the usual signs of iritis, a small nodule resembling a tubercle was present in the lower part of the iris. This nodule increased in size gradually, became purulent and ruptured into the anterior chamber which became filled with pus. Blastomycetes were recovered from this pus. At the onset of the iritis the fundus was normal. Histologic examination of the eye removed at autopsy showed a purulent keratitis and iritis with numerous blastomycetes. An incision had been made through the cornea for evacuation of the pus in the anterior chamber and apparently the corneal involvement was secondary to this. The ciliary body and choroid were essentially normal. Blastomycosis of the eyelids is frequent in association with other skin lesions. The conjunctiva is almost immune. Corneal ulcers have been reported which probably became infected with blastomycetes from lesions on the lids. Two cases have been reported in which blastomycetes were recovered from purulent intraocular exudation. In both of these the infection was probably through a corneal lesion. No definite case of metastatic intraocular blastomycosis has been reported previously. In the discussion of this paper Kronfeld stated that Stock had obtained tubercle-like lesions in the iris and metastatic retinochoroiditis following intravenous injection of blastomycetes into rabbits.

RADIOLOGY

UNDER THE CHARGE OF
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The Value of Roentgenography in the Diagnosis of Congenital Syphilis.—Material reviewed in this study by VOGT (*Am. J. Roent. and Rad. Therap.*, 1931, 26, 96) consisted of 109 infants under 2 years of age and mostly under 1 year. Blood Wassermann reactions were recorded in 91 and found positive in 83, or 91.2 per cent. Eight were negative or doubtful. The roentgenologic examination revealed bone lesions in 95 cases or 91.3 per cent, and in 71.1 per cent the bone changes were definitely diagnostic. The changes readily recognized and of chief diagnostic importance were: (a) Bone production exhibited as subperiosteal thickening; (b) bone destruction or osteomyelitis, and (c) disturbance of growth. Subperiosteal thickening was most common. It must be distinguished from periostitis due to other infections, particularly tuberculosis, and from the pseudoperiostitis seen in rickets. Dactylitis, which is really a periostitis of the phalanges, was noted in 16 cases. Osteomyelitis, evidenced by bone absorption and usually accompanied by new bone formation, was found in 63 per cent of cases. Usually it occurs at or near the ends of the long bones. A special type of osteomyelitis appears as bilateral semilunar defects at the upper ends

of the tibiae medially, adjacent to or just below the epiphyseal lines; Vogt regards it as pathognomonic of lues. Growth disturbance may be manifested by a dense narrow line at the ends of the diaphyses, with a parallel zone of diminished density.

Gall Stone Obstruction of the Duodenum.—A case in which the duodenum was completely obstructed by a large gall stone is reported by CRANE (*Am. J. Roent. and Rad. Therap.*, 1931, 26, 92). The shadow of the barium mixture ended abruptly just anterior to the duodeno-jejunal flexure, and the entire duodenum was dilated. In addition, the opaque mixture entered and depicted the common duct, some of the hepatic ducts, the cystic duct and the gall bladder. On reviewing the literature of the last 8 years, the author found 4 other cases of duodenal obstruction by gall stones, and 26 of similar obstruction in the small bowel beyond the duodenum.

Irradiation Treatment of Myoma of the Uterus.—Two hundred and eighty-four cases of uterine myoma were treated by SCHREINER (*Radiol.*, 1931, 17, 265). The size of the tumor was definitely influenced in 85 per cent, with regression to normal or at least a diminution to half the original size. Bleeding was controlled in from 96 to 100 per cent. Of the cases treated 98.5 per cent became symptomatically well. The menopausal symptoms—neurosis, hot flashes, sweating—with few exceptions did not seem to be any more severe after irradiation than in the average menopause.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Deafness in Trichinosis.—BOSCH (*München. med. Wchnschr.*, 1931, 78, 436) reports the case of a female, aged 51 years, who was admitted to a hospital with a trichina infection, 23 days after ingestion of ham from bears. Her symptoms comprised drowsiness, pains in the muscles and stiffness; blood examinations revealed an eosinophilia and demonstrated the trichinae. Two weeks after eating the bear flesh she first noticed deafness. Ten days after admission she was totally deaf; air and bone conduction were both lost; it was impossible to carry out the Weber or Schwabach tests. No abnormality could be detected in the ear passages or tympanum; the nose and throat were also healthy. A complete otologic examination was carried out every 3 days and a slow improvement became evident. After she had been in the hospital about a month, she was able to understand vowels and syllables shouted directly into her ear. The author regards the deafness as due to toxic acoustic neuritis rather than to a direct implication of the eighth nerve by the trichinae.

The Glucose Tolerance Curve in Epilepsy.—MACKAY and BARBASH (*J. of Mental Science*, 1931, 72, 83) state that while there is no typical glucose tolerance curve in epilepsy, a high percentage of epileptic patients present a glucose tolerance curve of a definitely subnormal type. The writers have attempted to correlate the type of epileptic (viz., irritable, confused, demented) with the blood-sugar level, but have been unable to determine that there is any such relation. Similarly they have been unable to establish any definite relation between frequency of fits and the blood-sugar level. The comparatively high percentage of cases with renal glycosuria in their series is worthy of note.

Curable Forms of Purulent Meningitis of Traumatic Origin.—BREGMAN and KRUKOWSKI (*L'Encephale*, 1931, 26, 110) find that meningitis is one of the most fatal complications of fracture of the skull. They present, however, 3 cases which recovered. In the first case, coliform bacilli were found in the cerebrospinal fluid, in the second case hemolytic streptococci, while in the third the fluid, although purulent, remained sterile. In the first and third cases a fixation abscess produced by an injection of turpentine appeared to have a beneficial effect.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Protective Measures of the State of California Against Botulism.—In a Cutter Lecture delivered by Harvard Medical School MEYER (*J. Prev. Med.*, 1931, 5, 261) summed up the developments preceding the organization of scientifically controlled canning procedures and their effect on the incidence of botulism in the United States. He states that food commercially preserved in the United States has not been connected with any of the recognized cases of botulism since 1925, therefore the processes of canning should be under official supervision in every state of the Union. In the 193 single and group cases of botulism occurring over a period of approximately 30 years 131, or 68 per cent, with an average mortality of 65 per cent, were caused by home-canned or home-preserved food articles, usually vegetables. Understerilization or inadequate curing have with monotonous regularity been the prime factors. To prevent the occurrence of tragedies due to poisonous string beans or corn is one of the pressing problems. Irrespective of the fact that botulism is one of the few diseases which can be readily avoided, groups of people continue to ignore the two following simple rules: (1) All home-canned vegetables and other nonacid foods should be thoroughly boiled before use. (2) The person who opens the container and prepares the contents for the table should be familiar with the standards of quality and should ruthlessly discard

any product which has leaky lids, an "off odor" or other signs of spoilage. Public health workers have been led to advocate the preservation of nonacid foods by drying, by curing in 10 per cent brine or by pickling in acidified brine. Aside from being simple and inexpensive, these methods have the one great advantage that the food is "not ready to be served" from the jar, but requires thorough soaking in water and sometimes subsequent boiling—the greatest safety device against botulism. Until there is an end to the custom of serving home-canned string beans and other vegetables cold as salads, often heavily seasoned with vinegar or mayonnaise dressings, which disguise any suspicious odors, botulinum intoxications may be anticipated. Every farmer's wife feels qualified to preserve vegetables in a glass jar. Spoilage is frequently so slight that even a competent observer may be misled. Moreover, the unboiled contents of many jars may have been consumed without bad effects, and thus a false confidence leads finally to the disastrous meal. Neither laws similar in character to that promulgated by Emperor Lex, in 905, for the purpose of preventing botulism due to blood sausages, nor official supervision, which is obviously impossible, but only the education of the masses as to the necessity for boiling all home-canned vegetables before use will in time prevent the frequent and needless deaths from these products.

Hepatitis by Streptococci.—McMAHON and MALLORY (*Am. J. Path.*, 1931, 3, 299) studied the pathologic changes in 5 clinical cases of streptococcic hepatitis. In 3 of these clinical cases the organism was demonstrated in the tissue, while in the other 2 the infectious genesis was assumed because of the lesions found. Five representative types of reactions are described: (1) Necrosis of liver cells particularly of the intermediate zones but spreading to involve the whole lobe with endothelial cell infiltration but no abscess formation. (2) Extensive focal necrosis of liver cells with endothelial cell infiltration, the mass of the liver, however, remaining normal. (3) Lesions uniformly distributed throughout the organ consisting of a zonal degeneration involving the periphery of the lobules but not those cells immediate to the portal areas. (4) Great proliferation of the bile ducts with atypical cells and increase in the interstitial tissue with the original lobular architecture displaced. (5) Minute grayish areas made up of numerous bile ducts but devoid of liver cells, while the portal vessels were still present. A pure culture of *Streptococcus hemolyticus* which had been isolated from a patient with scarlet fever was used for animal experiments. An injection was made into the mesenteric vein of rabbits with aseptic technique. These all had positive blood cultures after 12 hours. One rabbit died in 18 hours with numerous streptococci in the liver. Another dying in 24 hours showed fewer bacteria, while in one killed after 48 hours very few streptococci were to be found and in the animal killed after 5 days no organisms were to be found and very little evidence of damage. All showed however, some degree of focal necrosis, which was not limited to the central vein areas thus differing from chemical and bacterial toxemias. The authors would not attribute an infectious origin to all liver cirrhoses but they emphasized the similarity of the lesions resulting from streptococcic infections to that of the healed stages of acute yellow atrophy, and suggest that in many cases of the latter sufficient search might reveal a possible streptococcus etiology.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Germicidal and Therapeutic Applications of Soaps.—WALKER (*J. Am. Med. Assn.*, 1931, 97, 19) states that soaps are strongly bactericidal against pneumococci, streptococci, meningococci, gonococci, diphtheria bacilli, influenza bacilli and *Spirochaeta pallida*. Their activity against these organisms compares favorably with that of many of the recently synthesized chemicals. When properly used for cleaning the hands or for the washing of eating utensils soaps are undoubtedly potent factors in preventing the spread of diseases due to these organisms. The action of soaps as germicides is, however, limited by the fact that they do not destroy staphylococci and typhoid bacilli. Renaud has recently found 2 per cent solutions of sodium oleate beneficial as an irrigation and wet dressing for ulcerated surfaces.

The Epidemic of So-called Ginger Paralysis in Southern California in 1930-1931 SMITH and ELVOE (*U. S. Pub. Health Rep.*, 1931, 46, 1227) have had occasion to study an outbreak of paralysis due to the use of illicit ginger extract as a beverage. They report that in spite of the wide publicity given to this form of poisoning, a year ago this new outbreak occurred in California, also a smaller one in Massachusetts. The outbreak referred to consisted of about 125 cases, and in every case there was a history of the use of Jamaica ginger extract bought from drug stores. Chemical tests showed the presence in each offending sample of the phosphoric ester of orthocresol, which chemical had been found in the earlier outbreak and accounts for the symptoms. Details of the chemical and pharmacologic studies are given, and the opinion is expressed that future outbreaks of the poisoning may be expected unless effective steps are taken to prevent the distribution of the toxic material.

Studies on Meningococci Isolated in the United States, 1928-1930 Serologic Classification and Geographic Distribution. BRANHAM, TAFT and CARLIN (*U. S. Pub. Health Rep.*, 1930, 46, 897) note the disappointing results of serum therapy in epidemic cerebrospinal meningitis in recent years and have studied types of meningococci prevalent in the later epidemics. About half the strains were well agglutinated by the commercial serums used, and most of the remainder of the strains were agglutinated by these serums in some degree. It is not implied that the agglutinability indicates therapeutic efficiency of the serums against this specific organism. More than 80 per cent of the strains recently

isolated fell into a group which includes the Groups I and III. The authors report that while small isolated outbreaks are often due to one type of meningococci, more extensive outbreaks may involve all varieties.

The Smallpox (Alastrim) Epidemic in Holland.—JITTA (*U. S. Pub. Health Rep.*, 1930, 45, 66) reports that a sailor arrived at Rotterdam ill, infected his wife and she in turn infected the only unvaccinated child in the family (4 children). There was an outbreak of 8 cases in a hospital. Much question existed as to the diagnosis for a time, and it was finally reported as "alastrim." The death rate in Rotterdam was 5.5 per cent but *nil* in the remainder of the country. Following the extensive vaccination there was an outbreak of postvaccinal encephalitis—168 cases with 14 deaths.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 11, 1932

The Effect of Amebicidal Drugs on Tissue Culture Cells.—MARY JANE HOGUE (from the Laboratory of Anatomy, University of Pennsylvania). Much work has been done on the effect of certain drugs on *Entamoeba histolytica* but little is known of the effect of these drugs on the tissues of the host. There are three drugs generally used in the treatment of infections of *Entamoeba histolytica*: emetin hydrochlorid, yatren (iodoxyquinolin sulphonic acid), and dihydranol (2 to 4 dihydroxy phenol-n-heptane). A fourth substance is being used by Dr. de Rivas. It consists of equal parts of glycerin and a 30 per cent solution of magnesium sulphate. These four amebicidal drugs were made up with Locke-Lewis solution in dilutions of 1 to 1000, 1 to 10,000 and 1 to 50,000. Emetine was also diluted 1 to 100,000.

Tissue cultures were made from small pieces of the intestine of embryonic chicks 7 to 9 days old. They were grown in hanging drops in Locke-Lewis solution for 2 to 3 days or until there were good growths of epithelium, mesothelium, nerves and fibroblasts. The Locke-Lewis solution was then withdrawn and the tissue culture was completely covered with a loop full of one of the diluted drugs. The effect of the four drugs in their various dilutions was then studied microscopically in a warm box.

It was found that dihydranol diluted 1 to 1000 kills the cells at once *in situ*. In the higher dilutions it injures the cells at first. Later the tissues adjust themselves to the new medium and form fairly normal growths.

Emetine hydrochlorid in all the dilutions used kills the tissue culture cells. They disintegrate and the hanging drop is a mass of debris.

Yatren diluted 1 to 1000 kills the tissue culture cells slowly. In the higher dilutions there is slight injury at first followed by fairly normal growths.

The de Rivas mixture of glycerin and magnesium sulphate is slightly toxic to the tissue culture cells in the dilution 1 to 1000 but they soon adjust themselves to the solution and normal growth follows. The higher dilutions do not affect the growth though at first there is a slight shrinking of the outermost cells.

A Study of the Gregory and Pascoe Modification of the Pettenkofer Reaction and Its Application to the Determination of Bile Acids in Bile.

—JOHN REINHOLD and D. WRIGHT WILSON (from the Biochemical Laboratory of the Philadelphia General Hospital and the Laboratory of Physiological Chemistry, University of Pennsylvania). The technique described by Gregory and Pascoe¹ does not yield the greatest possible amount of color obtainable from the cholic acids. An experimental study of the reaction between cholic acid, furfural, and H_2SO_4 was made in order to find the most favorable conditions, which proved to be the following: 12 NH_2SO_4 , 10.4 mg. furfural, 0.05 to 0.3 mg. cholic acid in a total volume of 8 cc. heated in 18-mm. tubes at 70°C . for 8 minutes. The solution was cooled 2 minutes and read colorimetrically against a standard containing 0.215 mg. sodium cholate in red light of about 6100 to 7000 Å. For the analysis of human bile the protein must be removed by precipitation with alcohol and heat. This is not necessary when dog bile is the material.

A spectrophotometric study of the blue color formed in the reaction showed a well-defined absorption band with a peak near 6700 Å. By the modified technique the light absorption was about twice as great as by the Gregory and Pascoe procedure. An attempt was made to obtain additional information concerning the interfering effect of other substances that might be present by heating dog bile with 12 NH_2SO_4 alone in the absence of furfural. Absorption spectra of solutions so treated indicate that some of the blue derivative of cholic acid is formed even in the absence of furfural, but that the absorption of bile heated under these conditions decreases rapidly from 6100 Å. upward, indicating that the filters should cut off light below this wave length. The effect of biliverdin cannot be eliminated by filters, but interference from this source is not significant if precautions are taken to check the oxidation of bilirubin.

Conjugated and unconjugated cholic acids give equimolar quantities of color. Through the kindness of Dr. Carl H. Greene of the Mayo Clinic, we were able to compare the acetic derivative of sodium desoxycholate with the color produced by cholic acid under the conditions of the modified method. The purest sample of sodium desoxycholate gave only slightly more color than the reagents alone, a second gave $\frac{1}{4}$ and a third gave $\frac{1}{2}$ of the amount of color yielded by an equimolar amount of cholic acid. It seems reasonable to conclude, therefore, that the color was due to impurities, perhaps cholic acid incompletely removed, and that the method is specific for the cholic acid series.

Induction of the Ear from Foreign Ectoderm in the Embryo of Amblystoma Punctatum.—C. L. YNTEMA (from the Laboratory of Anatomy, Yale University). The potency of ectoderm outside the ear region to form an ear was studied experimentally in the embryo of Amblystoma

¹ Gregory, R., and Pascoe, T. A.: J. Biol. Chem., 1929, 83, 35.

punctatum. Ectoderm from posterior to the ear rudiment, when transplanted to the ear region during the later neural plate stage, frequently formed functional labyrinths. In the early head process stage, power to form an ear from this ectoderm was lost. In experiments performed between these stages, labyrinths of intermediate normality developed.

The relative potency of different regions of foreign ectoderm to form an ear was determined by transplanting ectoderm from several different parts of the embryo into the ear region when the neural folds were approximating. The ectoderm from the region ventral to that of the ear was more labile than transplants from any of the other regions.

Experimental Studies in Gastric Physiology in Man: An Evaluation of the Rôle of Duodenal Regurgitation in the Control of Gastric Acidity (Boldyreff Theory).—HARRY SHAY, ALBERT B. KATZ and EUGENE M. SCHLOSS (from the Gastro-intestinal Clinic of the Jewish Hospital, Philadelphia). Since Heidenhain's observation that the pure gastric juice in the normal dog was secreted at an acidity of 0.5 to 0.6 per cent hydrochloric acid and particularly since its confirmation in human beings by Carlson, physiologists have puzzled over the mechanism involved in the reduction of this high acidity to the one ordinarily seen in gastric contents. Of the theories evolved to explain this reduction, that of Boldyreff has enjoyed the greatest popularity. Briefly this theory contends that the relatively strong gastric acid (0.5 per cent) entering the duodenum provokes an abundant secretion chiefly of pancreatic juice. At the same time the acid through its irritant action on the duodenal mucosa, causes antiperistalsis in the duodenum, which in turn carries back into the stomach the alkaline pancreatic juice. This regurgitated juice in the stomach reduces the gastric acidity to approximately 0.15 per cent at which concentration it may be tolerated by the duodenum.

We studied this mechanism in human beings, using as a measure of regurgitation the amount of bromsulphalein present in the gastric contents, after the intravenous injection of the dye.

Bromsulphalein when introduced into the blood stream is taken out almost quantitatively by the normal liver. From the liver it finds its way to the second portion of the duodenum by way of the bile. The dose of dye used throughout the studies was 5 mg. per kilo body weight. The patients selected represented the entire range of gastric acidity as determined by Ewald meal and by histamin. More than 60 determinations were made.

Before making these determinations with various test substances, all patients were first standardized: (1) For removal of dye by the liver (blood estimation); (2) for regularity of appearance time of the dye in the duodenum through duodenal tube; (3) for the concentration of the dye in the duodenal contents during 20-minute periods for 2 hours after the duodenal appearance of the dye; (4) for the elimination of the dye by the kidneys during the test period.

The above determinations were repeated three times on each patient.

Following this standardization the fasting stomach was intubated. After emptying the stomach in all positions, the proper amount of dye was injected intravenously. At the duodenal appearance time for the particular patient the stomach was again emptied in all positions. Following this the patient ingested the test meal. This consisted, on suc-

cessive days, of 200 cc. of tap water, 200 cc. of 0.2 per cent and 0.5 per cent hydrochloric acid, and of 1 and 5 per cent sodium bicarbonate. Five minutes after the test meal was taken, the stomach was again emptied in all positions. The amount recovered was mixed and measured. It was then returned to the stomach through the tube by gravity, excepting 15 cc., which was retained. Subsequently at 20-minute intervals for 2 hours, the procedure, as at the 5-minute interval, was repeated. Each specimen retained was then titrated for free and total acidity and for the amount of dye when present. Knowing the approximate concentration of the dye in the duodenum at the corresponding times, measuring the amount of gastric contents and determining the concentration of dye when present in the mixed specimen, enabled us to form a very definite idea of the amount of regurgitation that must have taken place.

While we do admit that duodenal regurgitation into the stomach may and does frequently take place, we cannot, from our experiments, ascribe any importance to this mechanism in the regulation of gastric acidity. The results of our experiments are in agreement with McCann, that the control of gastric acidity depends essentially upon some intragastric mechanism. Our experiments also suggest the possibility of acid absorption in the stomach. Experimental data is presented indicating the fallacy of dissociated regurgitation of the bile and pancreatic juice from the duodenum into the stomach.

Corrections

In the article by Mora and Greene on "Thyroidectomy for Thyrotoxicosis in Older People" in the January, 1931, number of this Journal the paragraph preceding the Summary on page 80 which now reads "One death occurred in the remaining 860 cases which comprised this series. The total mortality (7 deaths) of the entire series of 1060 cases, which formed the basis of this report, was 0.66 per cent" should read "Three deaths occurred in the remaining 860 cases which comprised this series. The total mortality (9 deaths) of the entire series of 1060 cases, which formed the basis of this report, was 0.84 per cent." A similar correction should be made in paragraph 11 of the Summary.

In the Progress notes for Therapeutics in the February, 1932, number of this Journal, the reference to the article by Winternitz on page 282 should be "Ztschr. f. Kreislaufforsch., 1931, 23, 452."

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ORIGINAL ARTICLES.

THE NATURE OF THE PHYSICAL SIGNS OF BUNDLE-BRANCH
BLOCK.*

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AND

DONALD McEACHERN, M.D.,

(From the Cardiographic Laboratory, Johns Hopkins Hospital and University.)

BUNDLE-BRANCH, or intraventricular, block is not an uncommon disorder of conduction in the heart. In a previous communication⁹ it has been reported as occurring in 9 of 100 unselected cases of cardiac disease, in all of which electrocardiograms were made. During the past 4 years it has been possible for one of us to see 50 cases of this condition in hospitals and practice. Moreover, bundle-branch block is doubtless frequently overlooked since in the absence of an arrhythmia there is often little to direct attention to its presence or to suggest the desirability of obtaining electrocardiograms.

With our present knowledge of the mechanism of auricular fibrillation, of extrasystoles, and of auriculoventricular block, it is possible, in the majority of instances, to recognize these disorders at the bedside. The recognition of bundle-branch block without the aid of galvanometric records would, in like manner, be a distinct advantage. Under such circumstances the clinician would be freed from the necessity of using the electrocardiograph in disorders of the cardiac mechanism save to verify his clinical diagnosis or to

* We are indebted to the anonymous donor of a fund for medical research for aid in this work

recognize certain rare abnormalities. In this paper an attempt is made to point out and to illustrate the phenomena by means of which, in the majority of cases, bundle-branch block may be recognized at the bedside.

During the course of observations on the exposed dog's heart, in which a branch of the His bundle had been cut, Eppinger and Rothberger⁴ and later, Smith¹³ noted that asynchronous contraction of the ventricles could be made out immediately after the experimental section: apparently, such an observation served to inform the workers that the operation had been performed successfully. The only previous attempts to demonstrate by mechanical methods that this phenomenon may be projected to the precordium were made, so far as we are aware, by Kauf⁸ and by Eppinger and Stoerk.⁵ In each of these contributions a spiked apex ventricular wave was shown to occur on the apex cardiograms from an individual with bundle-branch block. Reduplication of the apex impulse was felt by Eppinger and Stoerk⁵ and by Kauf⁸ in patients known to have this lesion. However, prior to the report by one of us,⁹ no one seems to have noted that this evidence of bundle block might be perceived in most cases by careful examination of the precordium and thus permit of a strictly clinical diagnosis. Additional points of value in the recognition of this condition were noted at that time and are here reemphasized.

Physical Signs. Examination of the precordium by the usual methods of physical diagnosis has shown the signs of bundle-branch block to be as follows:

TABLE 1.—PHYSICAL SIGNS OF 50 CASES OF BUNDLE-BRANCH BLOCK.

	No.	Per cent.
Visible apical reduplication	42	84
Palpable apical reduplication	40	80
Auscultation:		
Reduplication of first sound at apex	28	56
Asynchronous systolic murmurs	6	12
Single first sound and separated systolic murmur	8	16

The character of the physical signs and the frequency of their evidence in this series are very similar to those noted in the more limited report by King.⁹ We are, therefore, surprised that Hill⁷ who recently reported a series of 41 cases of bundle-branch block states that such signs are not found with any degree of constancy and that the diagnosis is not possible at the bedside. The auscultatory signs reported by Hill are very similar to those herewith described though they were encountered less frequently in his series: he found visible and palpable reduplication, however, in only 1 of a "few" cases in which special search was made for all the physical signs. No mention is made of the number of cases of the total series observed personally by Hill. In our experience, the visible and palpable reduplication of the apex thrust, and particu-

larly the combination of the two by inspection of the palpating fingers, are more constant (see Table 1) and more characteristic, and therefore more helpful in the diagnosis, than are the auscultatory findings.

The proportion of diagnoses of bundle-branch block made at the bedside and substantiated by electrocardiograms is similar to that of the smaller series of 9 cases reported previously. (Table 2.)

TABLE 2.—FIFTY CASES OF BUNDLE-BRANCH BLOCK.

	No.	Per cent.
Diagnosed clinically	34	85
Not recognized clinically	4	10
Suspected: not definitely diagnosed	2	5
	<hr/>	<hr/>
Number of diagnostic attempts	40*	100

Differential Diagnosis. Inasmuch as Hill was unable to find reduplication of the apex thrust by inspection and palpation and found reduplication of the first heart sound in only about one-fourth of his cases, it is natural that he was unwilling to make clinical diagnoses from insufficient data. Feebleness of the heart sounds or the presence of an apical systolic murmur were the commonest auscultatory signs in his series. It has likewise been our experience that faint, or indeed inaudible, sounds at the beginning of systole are frequently encountered and constitute a helpful diagnostic sign of bundle block. But this is one sign only and, as Hill points out, not characteristic of this condition alone. To establish a clinical diagnosis, the entire group of physical signs must be considered.

These signs are almost never encountered except in the presence of intraventricular block of some type, either complete bundle-branch block or a marked delay in intraventricular conduction. Certain cases of prolonged *Q-R-S* interval that do not show all the electrocardiographic features of bundle-branch block as defined by Carter³ exhibit physical signs that are identical with those found in bundle-branch block. Presystolic gallop rhythm, for obvious reasons, may be mistaken for bundle block and *vice versa*.

Among 9 cases that exhibited a prolongation of the *Q-R-S* interval but lacked the complete electrocardiographic picture of bundle block, systolic reduplication at the apex was seen in 7 instances and felt in 5, while suggestive auscultatory evidences were distinguished in 6 instances. It is clear, therefore, that we cannot hope as yet to differentiate clinically between complete bundle-branch block and other forms of marked intraventricular delay. It is our impression, however, that the physical signs may be more marked and that they probably are more constant in cases of complete bundle

* Of the 10 remaining cases 6 were seen after the electrocardiogram was known, while in 4 other cases there was a difference of opinion as to the diagnosis. During the course of these diagnostic attempts the erroneous clinical diagnosis of bundle-branch block was made in 6 cases in which the electrocardiogram showed the condition not to exist.

block than in the other group. We have studied the physical signs systematically in 50 cases of complete bundle block but our series of other forms of prolonged intraventricular conduction is too small to be of real value.

Presystolic gallop rhythm is the condition most likely to simulate the clinical signs of intraventricular block. Four years ago, one of us (King) in an attempt to distinguish the two conditions, laid down the following hypothetical features thought to be characteristic of each: on inspection and palpation, *presystolic gallop* is indicated by an apparently presystolic, apical lift or shock preceding a ventricular impulse that is normally sustained; *intraventricular block* causes a split in the main ventricular lift. Thus, the adventitious impulse in presystolic gallop is comparatively slight and early, in intraventricular block it is late and follows the main systolic thrust. On auscultation, *presystolic gallop* causes a sound preceding a first sound that is usually vigorous or that is replaced by a vigorous murmur; in most cases of *intraventricular block*, the sounds begin with systole and consist of two faint sounds replacing the usual single first heart sound: either this is heard or the sounds are inaudible or are replaced by one or two murmurs. Applying these hypotheses to the diagnosis of 100 unknown cardiac cases (among which were 9 instances of bundle block and 12 of presystolic gallop) the one condition was mistaken for the other only once. Among 44 cases of bundle-branch block (Table 2) the incorrect diagnosis of presystolic gallop was made in 2 instances, and by one of two observers in 2 other cases. Among 14 cases of marked presystolic gallop, the correct clinical diagnosis was made in every instance.

Marked hypertension is considered to conduce to presystolic gallop rhythm. Certainly it is true that presystolic gallop rhythm, when present, is nearly always associated with marked hypertension and may disappear entirely during the moments of lowered tension that follow administration of drugs such as the nitrites and nitroglycerin. Definite apical reduplication in the presence of hypertension may indicate either presystolic gallop or intraventricular block. Reduplication in the presence of a normal tension would make us suspect the presence of intraventricular block. The diagnosis of block should not be withheld because of the presence of hypertension, however, provided typical signs be present. Thus, among the 50 cases of bundle-branch block reported in this series there was a systolic blood pressure of 150 mm. Hg. or above in 26 instances (52 per cent). Three of these 26 cases had complete A-V dissociation and idioventricular rhythm with the customary high systolic and low diastolic readings.

The blood-pressure readings of the 50 individuals in this series are tabulated above (Table 3). In practically every instance, a given figure represents the average of a large number of readings made while the patient was under observation.

TABLE 3.—BLOOD PRESSURE IN BUNDLE-BRANCH BLOCK.

Case No.		Blood pressure.	Case No.		Blood pressure.
1		250/150	22		155/85
2		240/80	23		150/80
3		225/100	24		150/60
4	First admission	220/110	25		150/45
	Second admission	210/128	26	In 1928	150/50
	Third admission	200/130		In 1929	150/40
5		190/110	27		146/90
6	First admission	190/100	28		145/104
	Second admission	100/60	29		140/81
7		190/110	30		135/85
8		190/100	31		105/75
9	First admission	190/70	32	In 1928	135/80
	Later	155/90		In 1929	130/90
10	First admission	185/100	33		130/98
	Levelled to	160/100	34		125/80
	Second admission	240/100	35		120/80
	Levelled to	160/100	36		120/80
	Third admission	180/110	37		120/90
	Fourth admission	170/100	38		120/70
11		180/140	39		118/75
	Later	160/130	40		116/95
12	First admission	180-220	41		116/95
		120	42	In 1928	115/70
	Second admission	117/98		Second admission	120/75
				Present admission	140/80
13		180/75	43		115/70
14		176/105	44		110/90
15		174/75	45		110/70
16		170/110	46		110/70
17		170/110	47		110/60
18		170/100	48		110/60
19		170/100	49		105/65
20		166/86	50		98/70
21		160/110			

Excluding the 3 instances in which there was also *A-V* dissociation with idioventricular rhythm, systolic pressures of 170 mm. Hg. or above occurred in 17 instances; and of 200 mm. Hg. or above in 5 instances. These figures which are somewhat lower than those recorded by Hill⁷ and Herrick and Smith⁶ may be accounted for by the averaging of a number of successive readings in this series. A number of cases which were followed over a period of several years showed gradually increasing pressure while in others there was a gradual lowering of the pressures usually associated with the development of myocardial failure.

In the group with presystolic gallop rhythm there was nearly always marked hypertension, readings of 200 systolic and 120 diastolic mm. Hg. and above being not uncommon.

In attempting to evaluate the significance of physical signs, more error has resulted up to the present time from leaning too far toward the diagnosis of presystolic gallop in hypertension than from mistaking presystolic gallop for bundle block. We feel that the two conditions are different both with regard to mechanism and clinical signs. This point will be discussed later.

In 3 cases with characteristic physical signs and electrocardiographic evidence of intraventricular block there was also complete auriculoventricular dissociation. These cases aided materially in the elucidation of the relation of such physical signs to events in the heart's cycle, inasmuch as the signs were found to be quite independent of auricular activity.

Case Reports. CASE 1.—(A. S. J. H. H. Disp. No. J-12153.) White, male, aged 60 years. There was no history of past infection. Symptoms consisted of dyspnea, orthopnea, edema and morning cough. Examination of the heart revealed marked visible and palpable reduplication of the apex thrust. During ventricular diastole there could be seen slight but definite rhythmic precordial waves due to the auricular contractions. (Demonstrated by Dr. L. V. Hamman.) The independent auricular waves were also visible in the jugular veins. The first heart sound was of fair quality, followed by a soft systolic murmur. The auricular contractions were audible. The radial pulse rate was 36 per minute; blood pressure, 220 systolic and 70 diastolic; rhythm of pulse regular. There was general arteriosclerosis. Teleoroentgenograms of the heart showed: M. R., 7 cm.; M. L., 10 cm.; T., 28. Wassermann reaction of the blood was negative. Clinical impression was: Bundle-branch block, complete auriculoventricular block, hypertension. Electrocardiogram showed: Complete A-V block. Q-R-S interval, 0.14 second. Right bundle-branch block. This was the first case of auriculoventricular block combined with bundle-branch block that came under our observation. It appears to be of special importance in showing that the signs of bundle-branch block are quite independent of auricular activity.

CASE 2.—(G. B. U. M. H.) A white male, aged 69 years, suffered from dyspnea, orthopnea and edema. There had been infection with syphilis 27 years previously. Examination of the heart showed a visible and palpable reduplication of the apex thrust. On auscultation a single first sound was distinguished, and this was followed after an appreciable interval by a systolic murmur. Pulse at the wrist was regular, 49 per minute. Teleoroentgenogram showed slight cardiac enlargement. Blood Wassermann reaction was positive; blood pressure, 174 systolic and 75 diastolic. There was evidence of arteriosclerosis and emphysema. Electrocardiogram showed complete auriculoventricular dissociation; Q-R-S interval, 0.11 second; all R waves notched; auricular rate, 88; ventricular rate, 49. T waves in opposite direction to the main ventricular deflection throughout. The R waves did not indicate predominance of either levogram or dextrogram. This patient was seen by one of us (J. T. K.) after the electrocardiogram was known, hence a purely clinical diagnosis could not be attempted. The case is of interest because it shows that the physical signs which we have found in bundle-branch block may occur in other types of intraventricular block, *i. e.*, in cases showing prolonged intraventricular conduction time without the electrocardiographic picture of typical bundle-branch block. The case also shows, as noted in Case 1, that the physical signs of intraventricular block are not related to auricular activity.

CASE 3*—(G. B. J. H. H. No. 33820.) A male negro, aged 63 years, showed dyspnea, orthopnea and edema. He had pneumonia 29 years prior to admission and typhoid fever 21 years before. There was no other history of significant infection. Examination of the heart showed visible and palpable reduplication of the apex thrust, and definite reduplication

* This case is to be reported in full at a later date.

of the first heart sound, which was soft and faint. Auricular sounds were audible and auricular waves were seen over the precordium. Pulse was regular, rate 27 per minute. Blood pressure was 200 systolic and 80 diastolic; the blood Wassermann reaction was negative. Teleoroentgenogram showed: M. R., 5; M. L., 11.7 cm.; thorax diameter, 30 cm.; aorta dilated. There was generalized arteriosclerosis. Clinical impression before consulting electrocardiogram (D. McE.): Complete auriculoventricular block, bundle-branch block. Electrocardiogram showed complete auriculoventricular dissociation, predominant levogram, right bundle-branch block with $Q-R-S$ interval, 0.14 second. At a later date there was a return to normal sinus rhythm with typical electrocardiographic evidence of right bundle-branch block. The clinical signs of bundle-branch block disappeared however. The reason for this is not apparent, but we observed this to occur in several cases that have been under observation for long periods of time. Hill⁷ noted several similar instances in his series.

These 3 cases offer strong evidence that there is no necessary relationship between auricular contraction and the physical signs of intraventricular block. The second case suggests that such physical signs may be found in instances of prolonged intraventricular conduction time that do not show the complete electrocardiographic picture of bundle-branch block. A number of cases of this type have been met with.

In establishing the correctness of the clinical diagnosis in these cases, the electrocardiogram has been the final arbiter and, save for 5 instances referred to below, the criteria of Carter³ have been strictly adhered to, viz.: (1) Prolongation of the intraventricular conduction time to 0.10 second or beyond; (2) slurring or splintering of the $Q-R-S$ complexes;* (3) a predominant levogram or dextrogram; (4) T waves of opposite sign to the main ventricular deflection in Leads I and III.

The aforementioned 5 cases, included in the series of 50 cases, all of which were diagnosed clinically as bundle-branch block, exhibited electrocardiograms that were levograms and that satisfied all the above criteria save that slurring of the $Q-R-S$ complexes was absent. The significance of such electrocardiograms is in debate at present. There would seem to be increasing evidence that curves of this type indicate block in the right bundle rather than simple left ventricular preponderance. Indeed, Luten and Grove¹² to whose paper the reader is referred for a discussion of the subject, consider that curves of this character, with $Q-R-S$ of *normal* duration are indicative of impaired conduction in the right bundle. Without entering the polemic on the subject, we suggest that some value may reside in the clinical observation that, of 5 such cases, all exhibited the clinical signs of bundle-branch block.

* In view of the recent work of F. N. Wilson and his collaborators (P. S. Barker, A. G. Macleod and J. Alexander: Excitatory Process Observed in the Exposed Human Heart, Trans. Assn. Am. Phys., 1929, 44, 125) it should be explained that the interpretation of electrocardiograms in this report has been made in conformity with the previous standard. For example, upright $Q-R-S$ complex in Lead I and inversion of same in Lead III has been considered indicative of right-side block.

Of additional interest are 7 cases in which auricular fibrillation and intraventricular block were present coincidentally. It is reasonable to assume that auricular activity played no part in the production of the clinical signs of bundle-branch block in these cases. The correct diagnosis of bundle-branch block was made clinically in 5 of the 7 cases. On the other hand it is doubtful whether a typical presystolic gallop sound ever persists in cases of hypertension following the onset of auricular fibrillation.

In an effort to illustrate the reduplicated thrust in cases of bundle-branch block, attempts were made to obtain polygraphic tracings from the apex and from the carotid. It was hoped that in this manner it would be possible also to determine which ventricle was being activated first. After many trials, however, it was found that the apparatus failed to inscribe the mechanical events with sufficient rapidity. By fastening a light straw upon the chest over the region of the apex impulse, it was found that the phenomena occurring at the apex could be demonstrated easily in the movements of the straw. This has proved a valuable method of presenting the signs objectively before groups of students. It has been possible to record the double apical thrust graphically both by cinematograph and in apex cardiograms.

For the latter purpose, the patient was placed in the recumbent position between the galvanometer and the recording camera of a Hindle electrocardiograph, the chest was exposed and a light broom straw was fastened by adhesive tape or by plasticene to the chest wall in the region of the apex impulse. The straw intercepted the beam of light from the electrocardiograph and its shadow was recorded on the film beside that of the galvanometer string. Simultaneous mechanical and electrocardiographic records were therefore made upon the film with the benefit of the same time marker.

No accurate analysis can be made of the time relationship of the various mechanical events in the cardiac cycle as inscribed in such records. Even the cardiograms recorded optically with the more sensitive capsules of Frank have variable degrees of lag due to slow or inadequate transmission of the mechanical events in the heart to the tissues of the chest wall. For purposes of illustration, however, the apex cardiogram is of value and for this reason records were made on a number of normal individuals and on patients with bundle-branch block and with presystolic gallop rhythm. No difficulty was experienced in recording the phenomena when such were visible or palpable over the precordium.

Records from normal individuals were obtained with some difficulty owing to the indistinctness with which mechanical events in the heart are transmitted to the precordium. Such records showed monophasic and diphasic curves of low amplitude which commenced 0.05 to 0.15 second after the beginning of *R* and which were complete by 0.27 to 0.50 second after *R*. No bifid character was noted



Fig. 1.—(8616.) Electrocardiogram and apex cardiogram (with Lead II) from control series. The subject was a male, aged 24 years, with rheumatic mitral stenosis and insufficiency and aortic insufficiency. No gallop rhythm. Electrocardiogram shows pre-dominant levogram, $Q-R-S$ 0.08 second. Apex cardiogram shows a normally sustained systolic plateau commencing 0.04 second after R and ending 0.42 second after R . The notch on descending limb was associated with a palpable diastolic shock apparently due to valve closure.

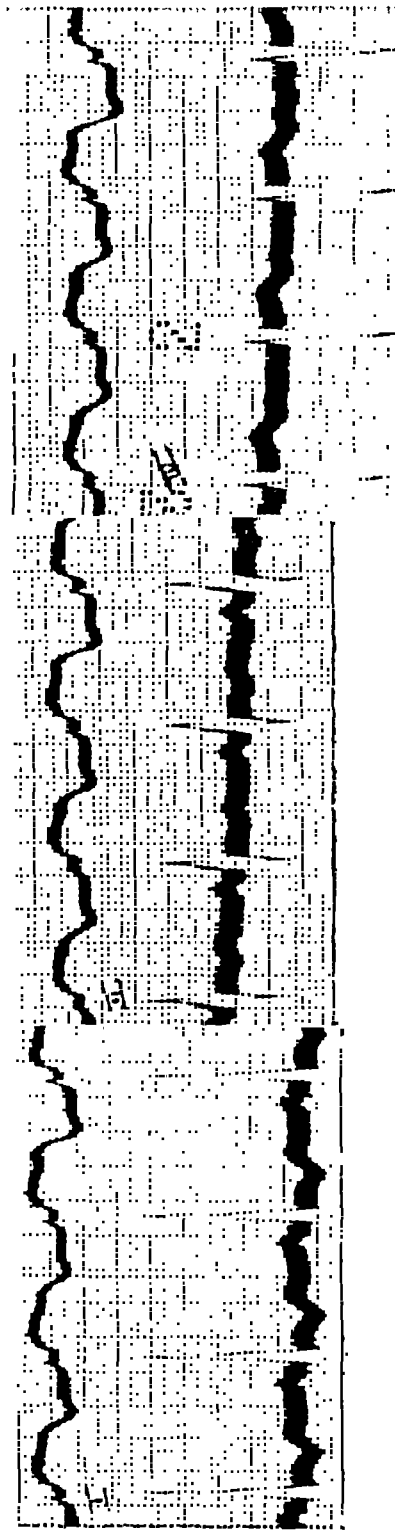


Fig. 2.—(8779.) Electrocardiogram and apex cardiogram from a patient with presystolic gallop rhythm. Blood pressure, 240 systolic and 140 diastolic. Electrocardiogram shows predominant levogram. $Q-R-S$, 0.1 second; T , I inverted; T , III upright. Cardiogram shows a series of high and long positive hummocks. On the upstroke of each there is a short positive deflection. This commences 0.02 to 0.03 second before R and is complete at 0.02 second after R . The further abrupt rise of the hummock commences 0.08 second after R . The hummock ends 0.52 to 0.56 second after R .

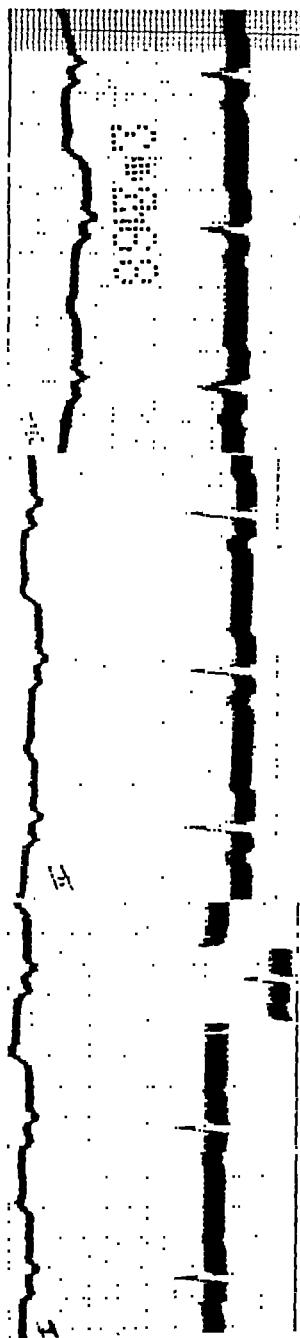


FIG. 3.—(8943.) Electrocardiogram and apex cardiogram from patient with presystolic gallop. Blood pressure, 186 systolic and 160 diastolic. Electrocardiogram shows $Q-R-S$, 0.08 second. Slight slurring of $Q-R-S$ in all leads. T , I upright; T , II and III biphasic. Apex cardiogram shows series of long negative waves preceded by a sharp negative deflection which commences 0.07 second before R and is complete by 0.03 second after R . The systolic plateau then commences and persists until 0.52 second after R .

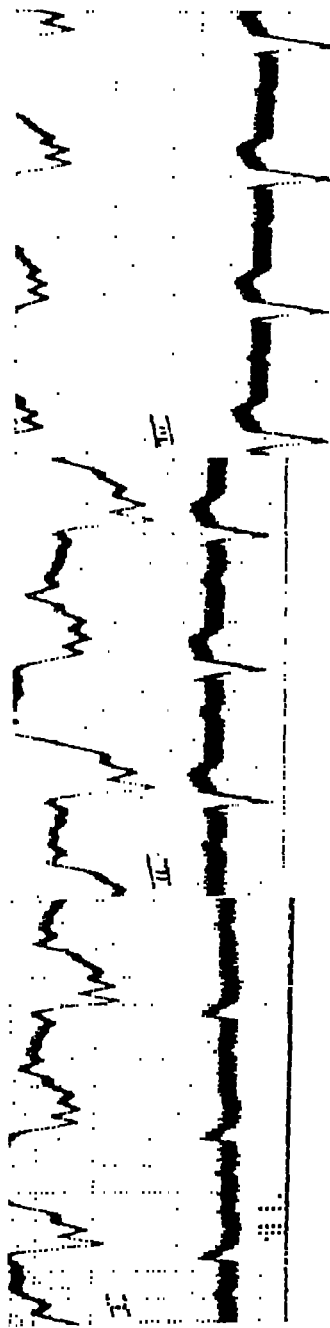


FIG. 4.—(9295.) Electrocardiogram and apex cardiogram from patient with right bundle-branch block. $Q-R-S$, 0.13 to 0.14 second. Cardiogram shows reduplication of the large negative systolic wave.

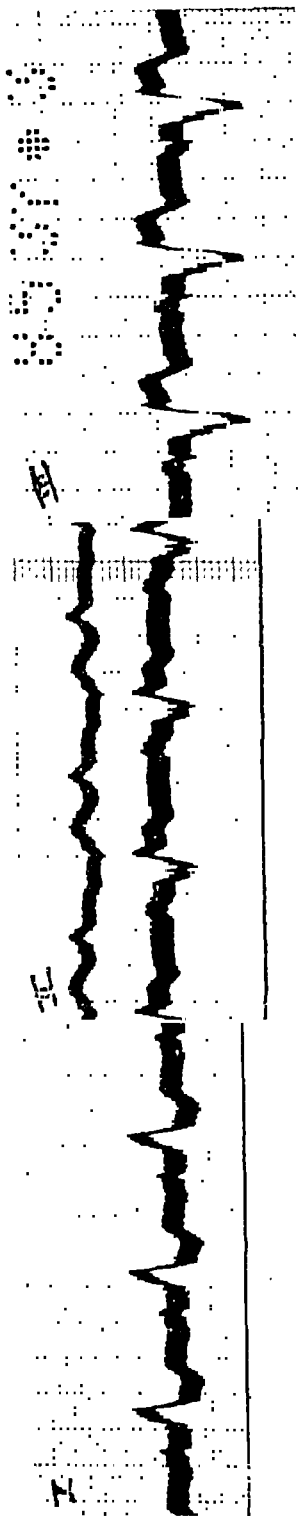


FIG. 5.--(S537.) Electrocardiogram and apex cardiogram from patient with right bundle-branch block. $Q-R-S$, 0.14 second. Cardiogram shows series of long positive waves of bifid character. First component commences 0.1 second after R and lasts until 0.45 second after R when the second component commences and lasts until 0.65 second after R .

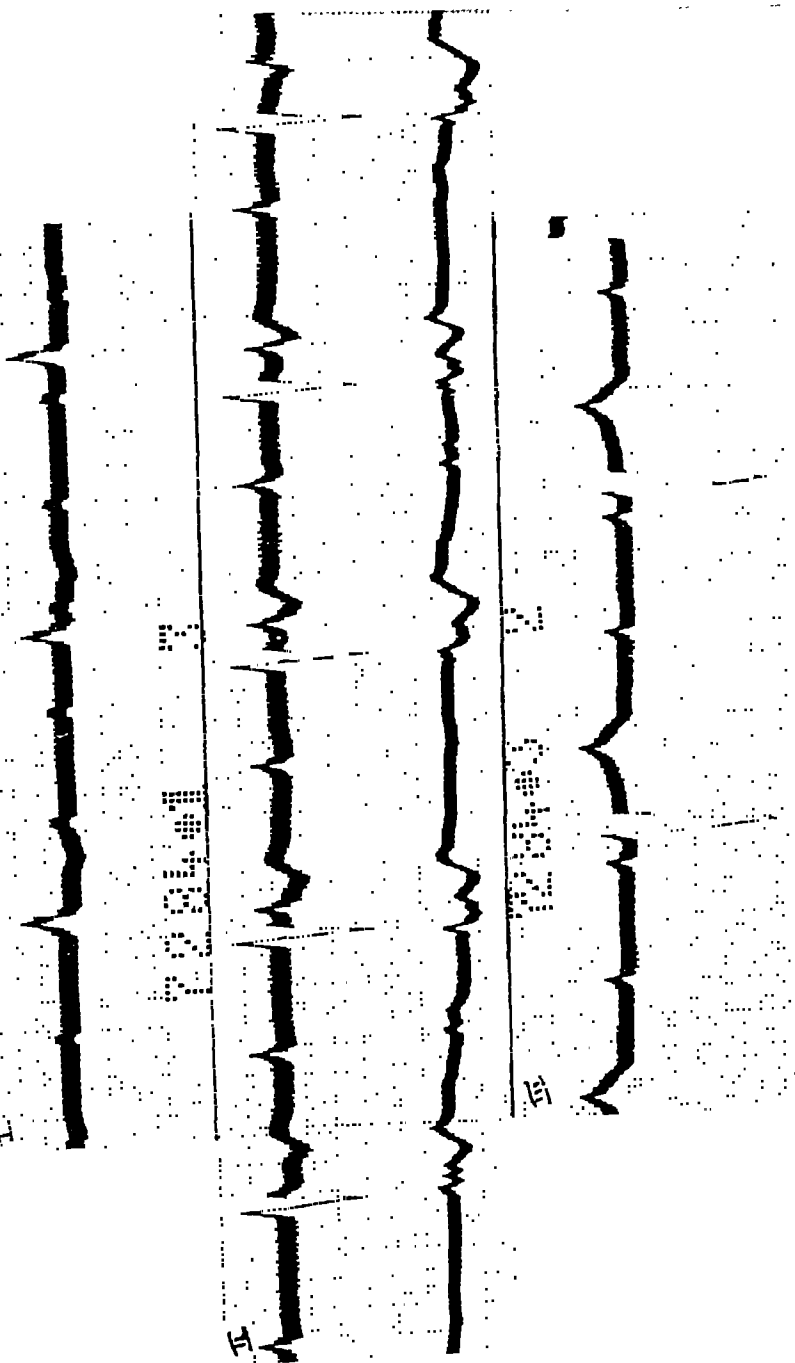


FIG. 6.—(7234.) Electrocardiogram and apex cardiogram of patient (Case 2) with right bundle-branch block and complete auriculoventricular dissociation. *Q-R-S*, 0.15 second. Auricular rate, 86. Ventricular rate, 29. Cardiogram shows a series of bifid, negative deflections associated with ventricular activity and commencing 0.06 second after *R*, the second component of each wave commences 0.26 second after *R* and is complete 0.6 second after *R*. Auricular waves can be seen. The fourth and fifth ventricular complexes (Lead II) of the cardiogram are entirely dissociated from auricular activity.

in the sustained apical wave during ventricular systole in any instance (see Fig. 1).

Presystolic Gallop. In this series of patients with presystolic gallop, the presystolic deflection of the straw could not be demonstrated in every instance. It was shown to be present, however, in those cases in which gallop was visible or palpable on the chest wall. No reduplication of the systolic thrust was noted in any instance. When seen, the presystolic deflection appeared 0.02 to 0.06 second before *R* and was complete by 0.02 second before *R* to 0.04 second after *R*. These deflections were similar to those visible and palpable upon the chest wall and, whatever their cause, occurred prior to the electrical evidence of systole. Figs. 2 and 3 are characteristic examples of these curves.

Bundle-branch Block. So far as we are aware, no attempt has been made to demonstrate the double apex thrust in bundle-branch block by means of apex cardiograms in a series of cases. The cardiograms of the individual cases reported by Kauf⁸ and by Eppinger and Stoerk⁵ show, however, bifid systolic waves. In the present series, apex cardiograms, in every instance save one, showed a double reflection which occurred during systole and which was indicative of the reduplicated systolic thrust visible to the naked eye during systole. The first component of this double systolic deflection commenced 0.06 to 0.10 second after *R* and lasted until 0.17 to 0.45 second after *R*, when the second component of the systolic deflection commenced and lasted until 0.44 to 0.62 second after *R*.

Typical curves are seen in Figs. 4 and 5. Of particular interest is the record Fig. 6 obtained from Case 1 (reported above) in which there was complete *A-V* dissociation and right bundle-branch block. In this case it was possible to demonstrate in the apex cardiograms not only the double systolic deflection associated with ventricular systole, but also the individual auricular beats which were transmitted to the apex as small rhythmic waves. The latter bore no constant relation to the ventricular deflections. It is not possible, therefore, to consider that contraction of the auricles is in any way responsible for the bifid character of the apical wave during ventricular systole.

Lewis¹¹ has recorded reduplication of the first sound in 4 cases of intraventricular block and has discussed its time in the heart's cycle. The beginning of the extra component was presystolic in each instance. What the relation of this sound reduplication to the waves on the precordium may be remains to be determined. One is tempted to attribute the waves noted in the present report to a theoretical asynchronism of the ventricles resulting from delay of the impulse to one ventricle. We have no proof of this, however, and we prefer simply to conclude that the signs we have discussed may occur independent of auricular systole and that they are due to some peculiarity of ventricular activity in the presence of intraventricular block.

AN UNUSUAL ATROPIN EFFECT ON VENTRICULAR TACHYCARDIA.

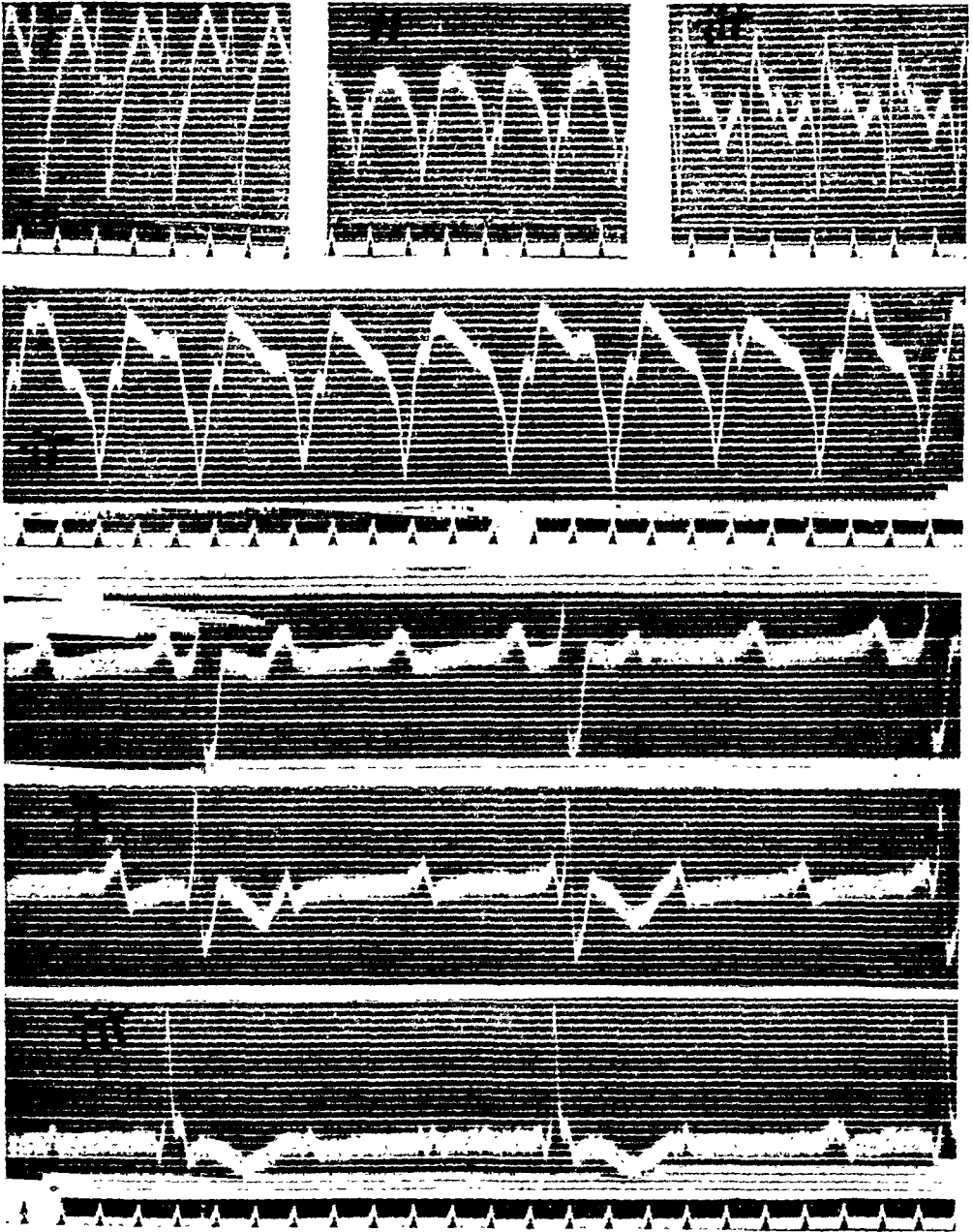
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It is generally accepted that certain disturbances in the auricles of the heart, such as auricular fibrillation and auricular flutter, are due to a circus movement.³ The most important factor in maintaining this circus seems to be the length of the refractory period of heart muscle. Influences that shorten the refractory period serve to perpetuate the circus and contrariwise, those that lengthen the refractory period tend to abolish the circus. There is a growing impression that tachycardia, ventricular in origin, is due to a similar circus movement in the ventricles. Much has been written concerning both experimental and clinical effects of quinidin on disturbances of this nature. Although quinidin has a double and conflicting action it often abolishes these movements. One effect of quinidin is to lengthen the refractory period which would tend to abolish it, while the other is to slow the speed of the impulse which would tend to maintain the circus. When the former predominates normal rhythm is established. Quinidin has been found to be frequently effective in restoring the normal mechanism in cases of ventricular tachycardia which, as has been stated above, is quite likely due to a circus movement in the ventricles.² It has been found also that atropin, mainly through its paralyzing effect on the vagus, lengthens the refractory period of the auricle and thereby tends to abolish the circus motion.⁴ The case reported below illustrates first, a partial effect of quinidin and second, a most striking and unique result of atropin on ventricular tachycardia.

Case Report.—A man, aged 56 years, entered the Hospital on May 12, 1928, in a typical attack of coronary thrombosis. An electrocardiogram taken on admission showed a ventricular tachycardia with a rate of 168. Quinidin sulphate was given in large doses and the tachycardia was slowed repeatedly but never below 108, as shown by repeated electrocardiograms. Following these temporary reductions in rate, it invariably rose again to 160 or 170. After 11 days of this sort of medication it was decided to try atropin, at a time when the ventricular rate was slowed to about 115 by quinidin, on the theory that by removing vagal effect the resulting increase auricular rate would enable the auricle to resume its control as the pacemaker. It was thought that if the auricular rate could be increased to a level greater than the ventricular a normal sequential rhythm might be restored. Accordingly, 0.002 gm. of atropin sulphate was given subcutaneously. The result was surprising. Within 7 minutes after the injection the pulse fell from a rate of 115 to 30 beats per minute. An electrocardiogram at this time uncovered a complete heart block with a ventricular rate of 30 and an auricular rate of 98. The heart sounds were distant and



Upper three tracings are Leads I, II, III, taken May 20, 1928, and show ventricular tachycardia with a rate of 180. The strip below this is Lead II taken May 22, 1928. The ventricular rate has been slowed to 115 by quinidin although tachycardia persists. Lower curves are Leads I, II, III, taken 7 minutes after 0.002 gm. of atropin had been injected and 30 minutes after previous tracing. They show complete heart block with an auricular rate of 98 and a ventricular rate of 30.



the patient was cyanotic and *in extremis* to such a degree that repeated doses of caffein sodiobenzoate were given. The ventricular rate remained between 30 and 35 for 27 hours and was then suddenly found to be 160 again. Following this the ventricular rate fluctuated between 25 and 190, despite two more trials of atropin and interrupted doses of quinidin, until the 16th day after admission. From this time on the rate did not fall below 130. The patient finally developed a bronchopneumonia and died 34 days after the onset of his attack.

This unusual atropin effect was entirely unexpected. When it was found that the patient had complete heart block it became clear that a normal sequential beat from auricle to ventricle was impossible. This result from atropin therefore must have been due to its action on the ventricle either through a direct effect on the muscle or indirectly through the vagus. There is experimental evidence to show that atropin through its paralyzing effect on the vagus increases the refractory period of auricular muscle⁴ and thereby might break up a circus rhythm. It is felt that this may well have been the mechanism involved in this case, although Drury¹ found that vagal stimulation did not shorten the refractory period of the dog's ventricle. If this is not the explanation of the atropin effect in the above case, it brings up for consideration the possibility of a direct action of atropin on ventricular musculature. It is also inferred that if the conduction apparatus had not been involved in the coronary attack, the ventricular tachycardia might likewise have disappeared under atropin with a restoration of normal rhythm. The unusual effect obtained from atropin in this case suggests that it might serve as an additional aid in restoring normal rhythm where a circus movement fails to respond to quinidin alone.

Summary. A case of coronary thrombosis was observed showing ventricular tachycardia with a rapid ventricular rate. The ventricular rate was frequently slowed by increasing doses of quinidin to 110 or 115, but the tachycardia could not be abolished. Immediately following 1 dose of 0.002 gm. of atropin sulphate this abnormal mechanism disappeared, uncovering complete heart block with a slow idioventricular rhythm. It is believed that the circus movement was broken up by atropin through its paralyzing effect on the vagus.

NOTE.—I wish to express my indebtedness to Dr. S. A. Levine for his aid in the preparation of this paper.

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CONGENITAL HEART DISEASE WITH MULTIPLE CARDIAC ANOMALIES.

REPORT OF A CASE SHOWING AORTIC ATRESIA, FIBROUS SCAR IN MYOCARDIUM AND EMBRYONAL SINUSOIDAL REMAINS.

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WE are reporting this single case of congenital heart disease because of the unusual number of congenital anomalies that it presented. The defects seen are not only numerous but some of them are distinctly rare.

Case Report. We know practically nothing concerning the history of the child or its parents. The child lived only 12 hours and necropsy examination was limited to the heart which was obtained by us with all the vessels cut quite close to the cardiac chambers.

Pathologic Examination. Except for a slight enlargement in the transverse diameter the heart is about normal in size. The longitudinal diameter measures 3.6 cm., the transverse 2.9 cm. The heart is divided by the interventricular groove into a large right, and a small left portion. The right ventricular chamber is considerably dilated; its wall measures 2.5 to 3 mm. in thickness in its lateral and apical portions; toward the base it becomes thicker, measuring 6 mm. The tricuspid valve is normal. The right auricle is also dilated but otherwise normal. The foramen ovale is completely closed. The fossa ovalis is very small and its markings almost completely obliterated. The type of closure with fibrous puckering would indicate that the closure had taken place early in fetal life. The pulmonary artery, which is enlarged for an infant of this size, issues from the right ventricle in its normal position. It measures 1.7 cm. in circumference and contains 3 normal cusps.

The left ventricle consists of a small chamber, closed on all sides except for its communication with the left auricle by an extremely narrow isthmus measuring 1 to 2 mm. in diameter. The boundaries of this chamber can be definitely outlined on the epicardial surface by the anterior and posterior interventricular grooves. The left ventricular muscle is about twice as thick as the right, measuring 7 mm. over its entirety. The width of the left ventricular wall diminishes the lumen of this small chamber to the size of a cherry stone so that its total contents could not exceed $\frac{1}{2}$ cc. On the cut surface of the left ventricular wall, varying in width from a fraction of a millimeter to half the thickness of the myocardium is a grayish-white area which is clearly demarcated from the normal muscle. It apparently consists of fibrous tissue which extends into the myocardium. Sections taken from histologic examination, will be described later.

The aorta is completely atresic. The ascending arch measures 2 to 3 mm. in circumference. The orifices of the coronary arteries open from its lower portion. At this level the lumen of the aorta tapers down rather suddenly

and immediately below this point it closes so that there is absolutely no communication with the left ventricle. The distal end of the aorta, although narrow, remains patulous. Its connections were unfortunately lost in the removal of the specimen. The ductus arteriosus could therefore not be examined. Two tiny budlike processes observed in the lower portion of the aorta near the point of origin of the coronary arteries are apparently the remains of the aortic valves.

The left auricle, like the left ventricle, is also small. It is about one-fifth the size of the right auricle. Attached to the left auricle by an isthmus is a very large left auricle appendage, the lumen of which, however, is rendered quite small by reason of a marked thickness of its wall. Entering the auricle are 4 pulmonary veins posteriorly and 1 vessel anteriorly, the connections of which cannot be definitely determined.*

The mitral valve is small, hypoplastic, and of entirely different appearance from that seen in the normal heart. It forms a diaphragm separating the diminutive auricle from the ventricle and the only communication between these two chambers is in the extreme anterior portion where the valve is deficient over a passage 1 to 2 mm. wide. There is no differentiation into anterior and posterior leaflets and no papillary muscles are observed. Two sets of what are apparently remains of chordæ tendineæ are, however, present.

Histologic Examination.—Left Ventricular Wall. Several specimens were taken from the left ventricular muscle in the region of the fibrous scar. The epicardium is moderately congested. The myocardium is of the infantile type but otherwise shows nothing unusual. The interesting feature was the presence of a zone of fibrous tissue extending from the endocardium into the muscle and varying in depth from about 0.5 mm. to $\frac{1}{2}$ the entire thickness of the wall. It seems to have a folding tendency, invaginating by many finger-like processes into the heart muscle. There is nothing unusual about this type of fibrous tissue. It is rather loose, and contains stellate and oval-shaped nuclei. A myxomatous structure is occasionally seen while in other fields a hyalinized sclerosis is present. The demarcation between the fibrous tissue and the heart muscle is not clear cut due to the extension of small threadlike processes into the myocardium for some distance.†

Another remarkable feature of this case is the presence of numerous circular and oval-shaped channels in the left auricular appendage and left ventricle, which at first we interpreted to be branches of the coronary artery. In some, the walls are thickened without great reduction in the size of the lumen; in others the lumen is reduced to a mere slit. Most of them contain erythrocytes and all are lined by a thin layer of endothelium. On closer examination and further study by serial section we decided that they were the remains of the sinusoids of the embryonic heart. Many can be traced to an endocardial origin, some apparently developing as infoldings or invaginations of the endocardium. The possibility of their being arteries was ruled out by their rather large numbers, large size, wall structure unlike arteries, and their presence chiefly in the inner half of the myocardium (a location where one would expect few coronary vessels). Moreover, section of the main coronary vessels and their branches show normal arterial structure. The thick walls which surround some of these spaces resemble very closely the thick, fibrous wall of the endocardium; the fibrous tissue

* It has been suggested that this vessel possibly communicated with the superior vena cava, as in the case of McIntosh.¹⁷

† Syphilis was considered as a possibility in the causation of the pathology noted. However, no evidence of syphilis could be observed in the sections, a diagnosis that was confirmed by the late Dr. Warthin, Professor of Pathology, University of Michigan, who kindly examined these sections for us.

is of a uniform character and there is no differentiation into intima, media, and adventitia. The fibrous tissue surrounding the walls of these spaces merges imperceptibly with the interstitial fibrous tissue of the myocardium. These channels which are the remains of a sinusoidal circulation, normally found between the muscle columns during an early stage of development of the heart, resemble to a great degree the findings observed in a heart described by Grant.⁷ Two small branches of the coronary arteries were traced by serial section to their union with a definite sinusoid (Figs. 6 A to E). The adventitia and media gradually blended with undifferentiated fibrous tissue, so that at the union of the sinusoid the original arteriole structure had largely disappeared. The intima and a few smooth muscle fibers are however preserved until the union with the sinusoid. Thus it appeared that blood passed through them from the coronary arterioles to be delivered to the cavity of the left auricle and ventricle (modified Thebesian system).

Left Auricular Appendage. The wall is unusually thick, and is composed of numerous interlacing muscular bundles widely infiltrated by fibrous tissue. Most of the latter can be traced as extensions from the thick fibrous wall of large blood spaces that appear to be anomalous vessels, but which are really infoldings of the thickened fibrous endocardium of the appendage. The blood spaces are apparently of the same type as those seen in the left ventricle.

Section of the coronary arteries reveals them to be normal. The right ventricular wall and right auricle present no abnormalities.

Summarizing, this specimen shows the following anomalies: Atresia of the Aorta, Hypoplasia of the Left Ventricle with marked Thickening and Localized Fibrosis of its Wall, Premature Closure of Foramen Ovale, Dilatation of Right Auricle and Ventricle, Diminutive Left Auricle, and Remains of the Sinusoids of the Embryonic Heart.

Course of Fetal Circulation in Aortic Obstruction. During fetal life the circulation is but little impaired by aortic stenosis. With stenosis of the aorta a smaller and smaller amount of blood will flow into the left atrium and to an increasing degree through the right ventricle. Therefore, the right ventricle, by reason of its increased work, will develop more quickly than the left ventricle which lags behind. With complete atresia of the aorta, the ascending aorta functions only as a coronary vessel from the aortic arch, and the blood can reach the aorta only through the pulmonary artery by the ductus arteriosus. There then exists in the words of Rauchfuss,²⁰ "one main chamber, the right ventricle, and one main arterial stream, the pulmonary artery." During these conditions, there is no noteworthy disturbance of the fetal circulation.

The disturbances in circulation begin with the taking of the first breath. With the inflation of the lungs a considerable amount of blood is directed toward the left ventricle. Since it is unable to go either through the aorta or through a patent ventricular septum, and since the foramen ovale is also closed, the blood remains stagnant in the left heart. This results in pulmonary congestion, pulmonary edema, and death.

Circulation in Aortic Obstruction After Birth. While unfortunately some of the vascular connections were lost in the removal of our specimen, it is possible in the light of what is known of similar cases

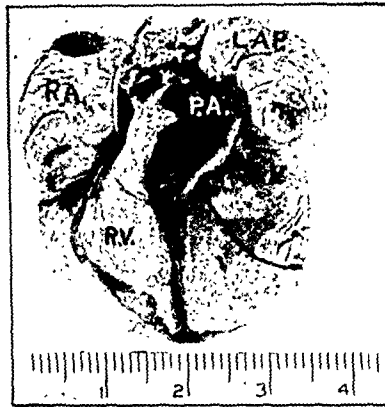


FIG. 1.—Anterior surface of the heart (actual size). The line in black represents the interventricular septum. *R. A.*, right auricle; *R. V.*, right ventricle; *L. A. P.*, left auricular appendage; *P. A.*, pulmonary artery (opened.)



FIG. 2.—The heart cut open from the left margin. The section opens not only the left ventricle but also the right ventricle in its lower half. The diminutive aorta has been slit open. *L. A. A.*, left auricular appendage; *P. V.*, pulmonary vein; *A.*, aorta; *X.*, lower end of aorta closed, does not communicate with ventricle; *L. V. W.*, left ventricular wall; *L. V.*, left ventricle; *F. S.*, fibrous scar in wall of left ventricle; *R. V.*, right ventricle forming apex and lower half of left margin of heart.

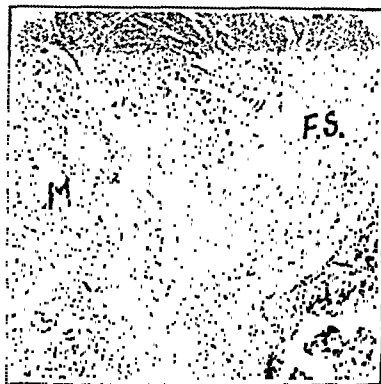


FIG. 3.—A section of the subendocardial scar in the left ventricle. Note the fibrous infiltration of the myocardium ($\times 69$). Many such extensions were noted. M., myocardium; F. S., fibrous scar.



FIG. 4.—The inner half of the myocardium, showing numerous sinusoids (S). ($\times 69$).



FIG. 5.—Several sinusoids with thick fibrous wall surrounding them ($\times 30$).

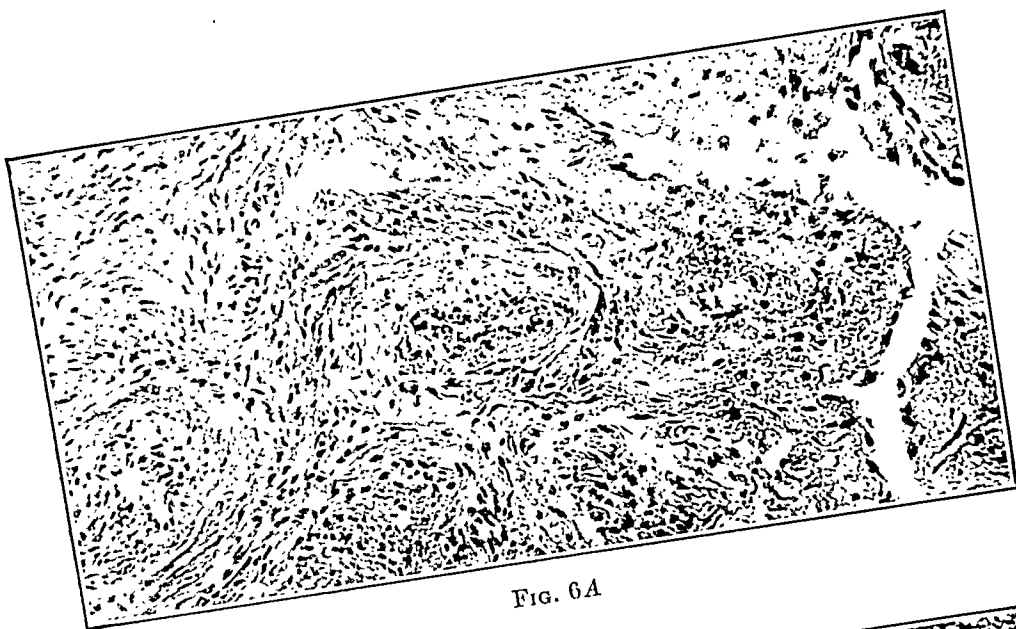


FIG. 6A

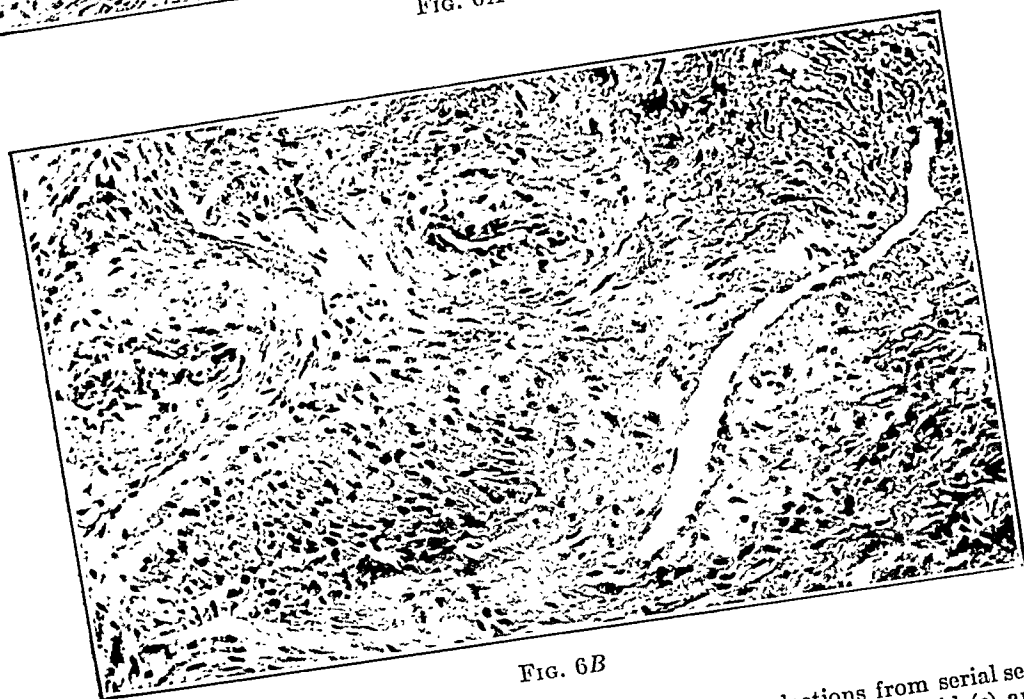


FIG. 6B

FIG. 6.—This figure is composed of five representative selections from serial sections showing the union of an artery with a sinusoid; A, shows the sinusoid (s) and two branches of the coronary artery (A). The arteries have a well-defined intima and media. The adventitia is beginning to lose its characteristics and tends to blend into the surrounding tissue ($\times 177$); B, the media and adventitia are indistinguishable from the surrounding tissue. One artery is approaching the sinusoid ($\times 177$); C, in this figure only the intima is clearly defined. The artery is now separated from the sinusoid by a thin wall of tissue ($\times 177$); D, this artery has occurred between the artery and the sinusoid. Note that the part that represents the artery is still lined with intima ($\times 177$).

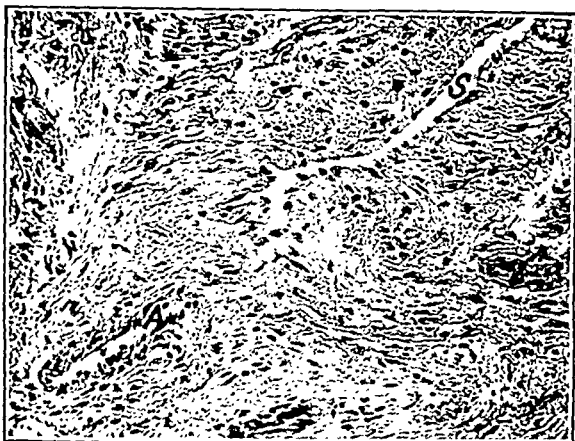


FIG. 6C



FIG. 6D



FIG. 6E

to reconstruct the probable course of the circulation. Venous blood entering the right auricle could not mix with that of the left auricle since the foramen ovale was closed. It therefore all proceeded into the right ventricle. From here the blood passed into the pulmonary artery, one branch of which went to the lungs, the other with the patent ductus, became the descending aorta. The body was, therefore, nourished practically entirely by venous blood. From the lungs blood reached the left auricle through the pulmonary veins. The fifth vessel of the left auricle may have communicated with the right heart in some manner, *e.g.*, with the superior vena cava as in the case of McIntosh,¹⁷ thus permitting the blood to leave the left auricle. A small amount of blood passed into the left ventricle from the left atrium but could not leave the former chamber through its normal openings. The only possibility of egress was back into the left atrium through the incompetent mitral valve. The complete closure of the ventricular and auricular septum prevented the admixture of arterial and venous blood. In our case the only possibility for this to occur was the communication of the fifth vessel in the left atrium with the right heart. However, this amount of blood would have been quite small. The multiple anomalies presented by this case were of such a nature as to be practically incompatible with life.

The duration of life in all cases of this type has been very short. Most live but a few hours or days after birth. Occasional cases have been reported which have lived several weeks.

This case can be discussed from three chief viewpoints: (a) Aortic Atresia; (b) Fibrosis of Myocardium; (c) Remains of the Sinusoids of the Embryonic Heart.

Aortic Atresia. We will discuss first the aortic atresia, since upon it is dependent the small left ventricle and with it is often associated fibrosis of the myocardium. Rauchfuss²⁰ (1878) collected 18 cases of aortic atresia with closed ventricular septum: 3 of his own and 15 of others. In all of his cases the foramen ovale was patent. Other cases have been reported by Ruge²¹ (2 cases), Shattock,²² Meyer,¹⁸ Haranger,⁹ Eppinger,³ Klepstein,¹³ Jurgen,¹¹ Theremin,²⁵ (15 cases) Kaiser,¹² von Zalka,²⁶ Ganefff,⁵ Bergman² and Hastings.¹⁰ Abbott¹ in her text in Osler's Medicine (1927) encountered aortic atresia 7 times in 850 cases of congenital heart disease, an incidence of (0.8 per cent). Of the total number of 50 cases of aortic stenosis and atresia collected by Ruge²¹ up to 1905, in only 5 cases was the foramen ovale completely closed as in our specimen.

Theories of Origin. Most writers, who have had similar cases, are of the belief that the origin of aortic atresia rests upon an infectious basis resulting in inflammation of the endocardium and the aortic valves, early in fetal life. This belief is based upon (a) the appearance of the aortic leaflets and the endocardium which resemble inflammatory processes observed in postnatal life; (b) the occa-

sional finding, as in the case of Klepstein,¹³ of fresh vegetation on the aortic leaflets; (c) the occasional observation of lymphocytic infiltration of the myocardium in instances of aortic and pulmonary atresia (cases of B. Fischer⁴ and von Zalka²⁶ (2 cases) and (d) the frequent presence of fibrosis of the myocardium (cases of Stiassny,²³ Mönckeberg,¹⁹ Fischer,⁴ Kochel,¹⁴ Ganef⁵, Ruge,²¹ von Zalka.²⁶) In only 3 of the 50 cases of aortic stenosis and aortic atresia gathered by Ruge²¹ in 1905, were all indications of fetal endocarditis absent. Rokitansky (quoted by Ruge²¹) was of the opinion that aortic atresia may also arise by unequal division of the truncus arteriosus through anomalous position of the aortic septum. This would result in a small portion being reserved for the aorta with the production of stenosis or even atresia of its lumen.

In our case, the presence of considerable localized areas of sub-endocardial fibrosis in the left ventricle and left auricular appendage, is suggestive of inflammation. We do not believe, however, that this finding alone is necessarily indicative of a previous inflammatory process; it might conceivably result from such a process as interference with blood supply, a condition which was certainly present in our case. The type and extent of the fibrosis in this case can be said to have been modified by a collateral circulation through the sinusoidal system.

Abbott¹ in 1 case observed calcification with cellular infiltration and a diffuse fibrosis which was often "myxomatous in character recalling Warthin's description of focal fatty degeneration associated with localized colonies of *spirocheta pallida*." She believes that syphilis plays a great rôle in the production of these changes. Gräfenberg⁸ has investigated numerous anomalies with reference to the presence of spirochetes. Although he found spirochetes in the viscera of 2 infants born with anomalies, in 22 other well-investigated cases no spirochetes were found. He concluded that syphilis plays a minor rôle in the causation of congenital anomalies.

The presence of myocardial changes with the formation of fibrosis in connection with aortic stenosis and atresia and pulmonary atresia is noted in the articles of Stiassny,²³ Mönckeberg,¹⁹ Fischer,⁴ Kochel,¹⁴ Ganef⁵, Ruge,²¹ and von Zalka.²⁶ Von Zalka studied the myocardium in 14 cardiac anomalies, 8 of which were due to arrest of development and 6 were due to stenosis or atresia of the pulmonary or aortic orifices. In every one of the latter he found the myocardial changes above described.

According to Rauchfuss,²⁰ the beginning of the disease during fetal life may be approximately determined by the size of the left ventricle. The smaller and more rudimentary the left ventricle the earlier is the narrowing of the aortic ostium produced. With narrowing and closure of the aorta in midfetal life we find a supplementary recess or space of the right ventricle which is due to its enlargement about and beneath the diminutive left ventricle, the

right chamber thus forming the apex of the heart. In atresia occurring in early periods of fetal life the right ventricle appears to be more generally enlarged and the left ventricle is smaller. Based on the description of this author, the atresia in our case probably occurred in the fifth month of fetal life.

Premature Closure of the Foramen Ovale. In our case the foramen ovale was early closed. (See reasons given above.) The premature closure of the foramen ovale is explained by Rauchfuss²⁰ as follows: In the course of the circulation of the fetus, the blood from the inferior vena cava goes through the patent foramen ovale to the left atrium and then to the left ventricle and finally to the aorta to nourish the head. With progressive stenosis of the aorta during fetal life, a stage is reached when the pressure relationships are about equal in both auricles, because of stasis of the blood in the ventricle with insufficiency of the mitral valve. When this moment is reached the foramen ovale will close in the fetus since the condition for its remaining patent, namely, the flowing of blood from the right into the left auricle, has ceased to exist. Rauchfuss²⁰ however, states that with atresia of the aorta the pressure on the foramen ovale from the left atrium is sufficient to reopen it if it has not completely closed, and distend its wall to the right. However, in the total of 50 cases of aortic stenosis and atresia collected by Ruge²¹ the foramen ovale was closed in only 5 cases. Why the foramen ovale closes in some and not in others is not definitely known. However, it is probable that if the pressure relationships are such as to permit closure to be maintained for some time fibrosis of such degree will occur that it cannot be later reopened.

Remains of Sinusoids or Intratrabecular Spaces of Embryonic Heart. The persistence of the intertrabecular spaces after birth is an extremely rare cardiac anomaly. As far as we are aware the only other heart in which this anomaly has been recognized is the one reported in a recent paper by Grant.⁷ In this paper he also mentions what may be another case of this anomaly in a malformed heart described by Mann,¹⁶ but there is no reference to it in the latter's text. Grant⁷ was able to trace connections between these spaces and the coronary arteries and presumably with coronary veins. We have been able in our case to trace their connections between branches of the coronary artery and the cavities of the left auricular appendage and ventricle (Figs. 6 A to E).

The embryology and physiology of the intertrabecular spaces have been investigated by Lewis¹⁵ and most recently by Grant.⁶ Very early in embryonic development (in rabbit embryos 8.5 mm. in length) the myocardium of the auricle is seen to be pierced by outgrowths from the endothelial lining of the auricle which form capillary spaces between the muscle and epicardium. Similar outgrowths later appear from the ventricle forming epicardial capillaries which are extensions from previously existing intertrabecular

spaces or sinusoids of the ventricles. Grant⁶ states that in embryos 17 to 20 mm. the intertrabecular spaces are observed as wide spaces between the growing muscle bundles, but their continuation into the compact myocardium cannot be distinguished from the fine ramifications of the veins and arteries there and all three structures together appear as a capillary network in that region. As the outer portion of the myocardium becomes more compact these spaces are practically obliterated, so that in older embryos they are best seen in the inner spongy portion of the myocardium. It seems to be quite generally agreed that the sinusoidal circulation is replaced by the coronary circulation. According to Lewis¹⁵ further development is marked by a continuous growth of the arteries and veins and by a regression of the intertrabecular spaces: the muscle columns coming together reduce many of the spaces to strands of endothelium without lumen. Grant⁶ has been unable to satisfy himself that actual obliteration takes place. According to him the outermost intertrabecular spaces are narrowed down by the compact myocardium to capillary tubes which are joined by coronary vessels extending inward from the epicardium. The capillaries arising from the central and inner intertrabecular spaces retain their connections with the ventricles. The ventricular communications persist in the adult as the Thebesian vessels of the ventricle.

It is difficult to explain here definitely the persistence in growth and the existence of the intertrabecular spaces which normally become reduced to capillaries. It is suggested that a high intraventricular pressure as a result of the cardiac anomaly, occurring at the time of the appearance of the sinusoids, led to a marked increase in their size. Another possibility to be considered is that the persistence and the marked development of the sinusoidal circulation was compensatory to hypoplasia of the coronary arterial circulation brought about by the atresia of the aorta.

Summary. Congenital heart disease in an infant is reported which presents a number of unusual and rare anomalies. These were: Atresia of the Aorta, Hypoplasia of the Left Ventricle with marked thickening of its wall, Hypertrophy, Premature Closure of Foramen Ovale, Dilatation of Right Auricle and Ventricle, Diminutive Left Auricle, and Fibrosis of the Myocardium of the Left Ventricle.

This case presented in addition a very rare anomaly: the Remains of the Sinusoids of the embryonic heart.

The incidence, theories of the origin of these anomalies and the resulting disturbances of the fetal circulation are discussed.

NOTE.—The authors wish to express their thanks to Dr. David L. Farley for permitting us to study and report this case.

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THE INCIDENCE OF THROMBO-ANGIITIS OBLITERANS IN BROTHERS.

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THERE are certain characteristics of thrombo-angiitis obliterans which are unique in that they are never encountered in other diseases. For instance, one of the mysteries of this ailment is its predominance in the male sex. Its predilection for Russian Jews

is also unique. Up to the present, no adequate explanation of this distribution of thrombo-angiitis obliterans has been advanced. I wish to call attention in the present communication to another unusual characteristic of this disease which has not heretofore been described in the literature nor in the textbooks on the subject.

Family Abstracts. In the examination of over 500 cases of thrombo-angiitis obliterans I have observed 3 families in which it occurred in brothers. In none of these families has there been any history of the disease in parents or grandparents on the maternal or paternal side, nor has there been evidence of the disease in other blood relatives.

Family 1. In the first family I shall describe, 3 brothers are affected with thrombo-angiitis obliterans. The parents of these young men were born in Austria and were apparently free from any evidence of peripheral arterial disease. As far as could be determined, there was no history of this disease in the grandparents or other blood relatives. The 3 young men were born in Austria and came to America in early childhood.

The oldest of the group is 34 and exhibits the mildest form of the disease.

His previous history is negative. He began to smoke at the age of 14 and consumed approximately 30 cigarettes a day up to the present. He first noticed symptoms at the age of 33 when, after walking long distances, he began to experience pains in the calf of the left leg of such severity as to necessitate rest before walking could be resumed. There were no other symptoms. Upon examination the left foot was found to be colder than the right and the left dorsalis pedis pulse could not be felt. There was moderate plantar ischemia¹ of the left foot and the oscillometer indicated a slight diminution of pulsation in the left foot. Over the right external malleolus there was a tender, cordlike, red area about 6 cm. in length which had the typical appearance of the superficial migrating phlebitis characteristic of this disease. The upper extremities were normal.

The younger brother, age 33, shows a more advanced stage of the disease. His previous history was negative and his symptoms started at the age of 24 with numbness of the left leg. Shortly after the onset there was noticed the typical migrating phlebitis on various parts of the left leg. Difficulty in walking was soon experienced, followed by severe pain in the left big toe. His condition had become steadily worse so that at the time of examination he could walk only three blocks and then was forced to rest because of a cramp in the right calf and a slight pain in the left leg. About a year ago he noticed recurrence of the migrating phlebitis but on this occasion it appeared on the right arm and since its disappearance the right hand is constantly cold and numb. Upon examination the right foot was found to be colder than the left. No pulses were felt in either foot and there was intense plantar ischemia of both feet, more marked in the left. Oscillometric index at the right ankle was 0, and the left ankle was 0.25. Both radial pulses were present, but upon elevation of both hands a cadaveric pallor developed in the right. The oscillometric index in the hands was 0.5 in the left, 0 in the right. There were no ulcerations nor signs of gangrene. There was intense rubor in both feet in the dependent position, more intense in the right. The nails of both feet were markedly atrophic.

The youngest brother, aged 29 years began to smoke at the age of 17 and has smoked about 15 cigarettes a day since then. His illness started with a typical superficial migrating phlebitis of both legs at the age of 24. The phlebitis disappeared after a few weeks and the patient felt well for about 2 years. He then began to experience pain in the sole of the left foot on walking. This condition has grown steadily worse, so that at the time of my examination he was hardly able to walk at all, and for the past

2 weeks had noticed a small black spot on the lateral aspect of the left big toe. There were no symptoms in the upper extremities. Upon examination the left foot was found to be colder than the right. Plantar ischemia was noted in both feet, more intense in the left. No pulses were felt in the left foot and the dorsalis pedis pulse was absent in the right foot. The oscillometric index at the right ankle was 1.5, left ankle 0. On the lateral aspect of the left big toe near the nail margin there was a bluish discoloration of the skin which, after a few days, became gangrenous and formed a small ulcer, which healed up after a few weeks of treatment.

It is interesting to note in this family the occurrence of migrating phlebitis in each case, also the onset of symptoms in the 2 brothers at the age of 24. In each instance smoking had been started at an early age and was continued for many years.

Family 2. Another family in which 3 brothers were affected with thrombo-angiitis obliterans was of Russian Jewish nationality. All of these were born in Russia and came to America at an early age. The oldest had been treated for thrombo-angiitis obliterans for a number of years in various hospitals throughout the city, where the diagnosis was definitely established. He did not develop gangrene, but at the age of 42 died suddenly, probably due to a coronary artery lesion.

Another brother died at the early age of 35 in a similar manner, probably as a result of cardiac involvement. He had been treated for thrombo-angiitis obliterans by some of the leading specialists in the city.

The third brother, who is now being treated by me for massive gangrene of the left foot, is now 40 years of age and has an advanced degree of thrombo-angiitis obliterans in both lower extremities. A few years ago he also had attacks of precordial distress and dyspnea which were diagnosed as coronary seizures.

All 3 brothers were heavy cigarette smokers. The parents and grandparents had no symptoms of circulatory disturbances of the extremities as far as could be determined.

Family 3. The third family in which I have observed the occurrence of thrombo-angiitis obliterans originated in Austria. The two members of the family who were affected with thrombo-angiitis obliterans were, however, born in America.

The oldest, aged 48 years, had one leg amputated at the age of 30 for gangrene due to thrombo-angiitis obliterans. The other leg was recently amputated in a southern hospital for the same cause.

His brother, aged 43 years, has an advanced case of thrombo-angiitis obliterans with massive gangrene of the left foot. There is also moderate involvement of the right foot. Both patients are heavy cigarette smokers. There is no history of circulatory diseases in the extremities of the parents or grandparents as far as could be determined.

Summary. The etiology of thrombo-angiitis obliterans is still unknown. There are, however, certain peculiarities in the disease which may have some bearing upon the underlying cause: (1) Its predominance in Jews; (2) its predilection for young males; (3) its association with cigarette smokers; (4) its occasional occurrence in brothers with no direct evidence of inheritance.

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ERYTHROMELALGIA AND OTHER DISTURBANCES OF THE EXTREMITIES ACCOMPANIED BY VASODILATATION AND BURNING.

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IN 1872 Weir Mitchell³ reported the case of a sailor who had a hitherto undescribed vasomotor condition of the feet. In 1878 he reported 5 additional cases. The characteristics were as follows: (1) There were attacks of bilateral or symmetric burning pain in the hands or feet; (2) the attacks were initiated or aggravated by standing, exercise or exposure to heat; (3) relief was obtained by elevation and exposure to cold; (4) during the attacks the affected parts were flushed and congested, and exhibited increased local heat; (5) the condition was refractory to treatment. These five basic criteria were postulated as necessary for the diagnosis of this condition. Mitchell applied to the condition the name "erythromelalgia," or "red, painful members." In his second communication he included his observations on 6 cases and 5 reports which he found in the literature. An analysis of the 6 cases Mitchell observed showed that in 3 the condition was bilateral, involving the feet; in 2 it was bilateral, involving the hands; in 1 case, unilateral. In 4 cases the attacks were aggravated or incited by exposure to heat or by exercise, in 4 they were relieved by elevation, in 3 by exposure to cold and concerning 1 case mention of relief was not made. In all there was congestion or engorgement during the attacks. Special mention was made of increased local heat during the attacks in 4 cases; no mention was made concerning 2, but it was implied that this feature was characteristic of all.

In the 5 cases Mitchell derived from the literature, with the exception of Veilpian's, the data were too incomplete to allow of adequate analysis. (Table 1.) Paget's case was not typical, in that cold and exercise produced pallor and numbness in the feet, followed by local heat and redness; this condition suggests a hypersensitive reaction to cold, such as is obtained in chilblains or cold allergy. In Graves' case the condition was not symmetric; one foot was affected at a time, and factors of relief and aggravation were not typical. In Stille's case the hands were livid, hyperesthetic, and there was clubbing of the nails. Although his notes were incomplete, peripheral neuritis is suggested. In the case reported by Greiner there was swelling and pain of the fingers and toes; relief was obtained by application of cold water. There was no evidence of loss of motor and sensory function, and recovery occurred in 3 months. In Case 10, seen by Mitchell himself, involvement was of the right foot, the patient was 82 years of age,

TABLE 1.—ANALYSIS OF CASES REPORTED BY WEIR MITCHELL (1878).

Case.	Age in years and sex.	Regions affected.		Factors in initiating attack.	Means of relief.	Increased local heat or congestion.	Response to treatment.	Comment.
		Feet.	Hands.					
1	40 M	Both simultaneously	Not stated	Exercise and heat	Elevation and cold	Present	Refractory	Red, tender spots on soles of feet; mucous membranes injected. Cushions of fingers congested. Distribution, blotchy and patchy.
2	35 M	Both simultaneously	Not stated	Exercise and heat	Elevation and cold	Present	Refractory	
3	58 M	Both simultaneously	Not stated	Exercise and heat	Elevation	Present	Refractory	
4	29 M	Not stated	Both	Exercise and heat	Elevation and cold	Present	Refractory	
5	M	Not stated	Both	Local pressure	Not stated	Present	Not stated	Reported by Stille; generalized redness; clubbed fingers.
6	29 F	Not stated	Both	Not stated	Not stated	Present	Not stated	
7	22 M	Both simultaneously	Both	Standing	Cold	Present	Recovered in 3 months	Reported by Greiner; muscular and sensory involvement, probably neuritis.
8	35 F	Both simultaneously	Not stated	Exercise and heat	Cold	Present	Refractory	Reported by Veilpian; numbness of parts.
9	16 F	One at a time	Not stated	Neither exercise nor heat	Cold	Present	Refractory	Reported by Graves, 1864; cyclic pain with spontaneous remission.
10	82 F	Right only	Not stated	Not stated	Not stated	Present	Responded to treatment for gout	Cerebral accident; severe continuous pain and swelling of right foot.
11	M	Both simultaneously	Not stated	Exercise and cold	Not stated	Present	Not stated	Reported by Paget; pallor, followed by redness and increased heat of feet.

and hemiplegia, which involved the left arm and the left leg, had occurred previously. Relief was obtained by means of treatment for gout. It seems impossible to accept these 5 cases as examples of erythromelalgia, and Mitchell was in doubt as to how to classify them. Mitchell also reported 5 cases in which there were painful feet, without redness or swelling, but with typical effects from heat and exercise. These he did not accept as typical examples of the disease, because visible flushing or congestion of the affected parts were absent and they are not included in the tables which accompany this paper.

Critical review of Mitchell's printed material convinces me that he described a clinical entity or syndrome of a primary form, which, to my knowledge, never had been reported previously. In the typical, acceptable cases 5 basic signs or symptoms that he emphasized were present. Mitchell did not accept, as characteristic, cases in which flushing and congestion were absent (his Cases 13 and 14), in spite of the presence of high surface temperatures in the affected parts. This is confusing, since local fever or increase in heat, with burning distress, may be present, without marked flushing or congestion. Phenomena of vasodilatation vary in degree, and the essential factor is increase in temperature rather than redness of the skin.* The important point is whether the surface temperature increases with, and parallels, the burning distress. If this is accepted as a modification of Mitchell's criteria the grouping of cases of erythromelalgia is more comprehensive, and the conception of the syndrome is clarified.

From subsequent reviews of the literature by Cassirer¹ and by May and Hillemand,² it is seen that nothing has been added that would allow one to change, to any great extent, the original concept that a vasomotor neurosis exists, as outlined by Mitchell. However, a survey of many of the cases in the literature makes clear that the original concepts of the disease have been lost sight of, and many and varied forms of vascular disturbance have been erroneously classified as examples of erythromelalgia. A review of the literature for the last 10 years reveals only 1 case that conforms to the criteria necessary for the diagnosis of erythromelalgia. The majority of the reported cases indicate the tendency to employ the term erythromelalgia to describe a symptom; for instance, erythromelalgia is spoken of as occurring in polycythemia vera, when the reporter means a secondary disturbance arising from vasodilatation. The term erythromelalgia is, strictly speaking, not accurately descriptive, and has led to confusion and mistakes in

* From more modern studies we have learned that increased local heat indicates dilatation of the arterioles, and redness, dilatation of surface capillaries and venules. These are not necessarily parallel; in fact, more often are disassociated than otherwise. Following sympathetic ganglionectomy the feet become hot, but redness of the skin is absent. Conversely, in the cold, red extremities of thromboangiitis obliterans there is arteriolar constriction and dilatation of capillaries and venules.

diagnosis, as a survey of the literature will show. Redness and pain of the feet are present in other conditions, as well as in erythromelalgia; for instance, in thromboangiitis obliterans, in localized arteriosclerotic disease when the feet are in the dependent position, in gout, in cellulitis of low grade involving the feet or hands and in certain cases of Raynaud's disease in the stage of recovery or over-reaction, in which the hands or feet become excessively hot and red. A more correctly descriptive name should embrace the concept of increase in local heat, or vasodilatation. Redness, flushing, or local congestion may vary widely or may be absent in the presence of arteriolar dilatation and hot extremities. In my grouping of cases I have followed this more concise interpretation of the disturbance.

The pathologic basis of erythromelalgia has not been established. Many and diverse changes in the peripheral nerves and vessels, and in the spinal cord have been described, none of which, however, leads to the belief that any characteristic lesion has been discovered.

Material and Methods of Study. A series of patients, whose major complaint was burning in the feet or hands, was hospitalized for study, thus minimizing the effects of changing environmental temperature. The purposes were: (1) To determine the relationship, if any, of the burning distress to the surface temperature of the affected part; (2) to study the variations in surface temperature and local symptoms in relation to posture, exercise and exposure to heat and cold; (3) in a small group of cases, by the method of inducing fever by injection of foreign proteins, to determine the thresholds for perception of the burning sensation in relation to surface temperature regions in which the burning was felt; (4) in 4 cases in which burning distress of a paresthetic type was present, associated with some degree of vasodilatation, by inducing spinal anesthesia to the point of total analgesia in the feet, to determine whether or not the pain could be relieved, and thus to obtain important information as to the origin of the pain, whether it was peripheral or central.

Eighty-one cases were studied, in all of which burning pain of the hands or feet was a prominent or disabling symptom. The following groupings were made: Group 1 included 10 cases which represented, I believe, true primary erythromelalgia. This gives an incidence of approximately 1 of every 200 cases of peripheral vascular disease seen at The Mayo Clinic. Group 2 was composed of 3 cases of primary unilateral disturbance of vasodilatation involving either the feet or hands. Group 3 was made up of 23 cases of paresthesia, with some intermittent vasodilatation of the affected part, but in which parallelism could not be demonstrated between the surface temperature and the burning distress. Group 4 included 27 cases of paresthesia, in which burning distress was present, the affected parts were cold, and periods of vasodilatation did not occur. Group 5 was constituted of 10 cases of polycythemia vera, with

bilateral or unilateral disturbances of vasodilatation of the extremities, in which the burning distress was the major symptom. Group 6 included 8 cases which could not be classified.

In addition, there was a number of cases of Raynaud's disease, in which, during periods of warm weather or under exposure to increased degrees of environmental temperature, the excessive amount of vasodilatation in the hands and feet frequently constituted rather severe distress. None of these cases was included in this study, because the underlying disturbance was clearly a vasospastic rather than a vasodilator condition. In this report will be presented the data on the cases in Groups 1 and 2.

Study of Group 1: Erythromelalgia. All cases except Case 3 (Table 2) exhibited four of the five basic signs and symptoms described by Mitchell. I have ceased to consider nonamenability to treatment as an essential characteristic. Localized flushing usually was present in some degree during the attacks, but that the sharp degree of vasodilatation was more decisive was evident by palpation and was proved by the rise in surface temperature, or by the marked increase in elimination of heat, as determined by the calorimeter. With subsidence of the attack there was a sharp drop in the temperature of the parts. In all cases the disturbance was bilateral either in the hands or feet, and in all the peripheral arteries were patent. The distress was uniformly instigated or sharply aggravated by heat, exercise or standing; relief was obtained by elevation or by local or general application of cold. In the more severe cases local congestion, pulsation in the veins and localized hyperhidrosis and hyperesthesia were observed during the stage of hyperemia. In none was any associated disease present, and the vasomotor condition apparently was primary. In Case 3 the effects of heat and cold were not present, and the disturbance was not always bilateral, but in other respects the observations were so definite that inclusion of the case was thought justifiable.

Case Reports. **CASE 1.**—A man, aged 57 years, whose case was the most severe in this entire series, exhibited in every respect the characteristic phenomena described by Mitchell. The bilateral attacks of burning of the feet had been present for 22 years. At first the condition had been intermittent, and complete relief had been obtained with rest, cold and elevation, but within a few years before the patient was seen at the clinic it had progressed to such a degree that almost complete and continuous disability was present. In the summer months, to obtain relief, he had lived on the banks of a river and had spent the days walking about on the wet sands. Wearing shoes or covering the feet had caused most excruciating pain. During the attacks marked congestion and increased local heat were present. At the clinic many and varied medical and surgical measures were tried without avail. The patient committed suicide 2 years after he was seen.

CASE 2.—A man, aged 27 years, gave a history of having had attacks of burning pain in the hands and feet for 6 years. He was not completely disabled. Local flushing was mild, but surface temperatures were high

TABLE 2.—SUMMARY OF CASES OF ERYTHROMELALGIA SEEN AT THE MAYO CLINIC.

Case	Age in years and sex.	Severity of attacks.	Parts affected.	Duration of complaint, years.	Bilaterality of condition.	Subjective symptoms.	Exciting factor.				Factor giving relief.			Color of parts during attacks.	Surface temperature of affected area.	Results and subsequent course.
							Hot weather.	Exercise.	Standing.	Elevation.	Cold water.	Rest.				
1	57 M	Definite	Plantar surface and dorsum of feet.	22	Bilateral	Burning, stinging	Yes	Yes	Yes	Yes	Yes	Yes	Flushed	Sharp increase	Suicide 2 years later.	
2	27 M	Definite	Distal half of soles of feet; heels; hands	6	Bilateral	Burning	Yes	Yes	Yes	Yes	Yes	Yes	Slightly flushed	Sharp increase	Markedly improved 5 mos. later	
3	34 F	Definite	Soles of feet; fleshy parts of hands	4	At times unilateral	Burning	No	Yes	No	No	No	Yes	Slightly flushed	Sharp increase	Essential hypertension; not followed.	
4	53 F	Definite	Both feet and hands	Many	Bilateral	Burning	Yes	Yes	No	Yes	Yes	Yes	Flushed	Sharp increase	Not followed.	
5	35 F	Definite	Both feet and hands	3	Bilateral	Burning	Yes	Yes	Yes	Yes	Yes	Yes	Flushed	Sharp increase*	Some improvement.	
6	55 M	Definite	Feet and great toes	Not noted	Bilateral	Warmth	No	Yes	No	No	No	Yes	Not noted	Increased to 36° C.	Four years later feet about normal.	
7	62 M	Definite	Pressure areas of soles of feet	12	Bilateral	Burning pain	Yes	Yes	Yes	Yes	Yes	Yes	Not definite	Marked increase	Practically unchanged 3 years later.	
8	54 M	Definite	Feet and legs	10	Bilateral	Burning pain	Yes	Yes	Yes	Yes	Yes	Yes	Red	Increased to 35° C.	Disappeared in 2 years.	
9	78 F	Definite	Soles of feet	4	Bilateral	Burning distress	Yes	Yes	Yes	Yes	Yes	Yes	Red	Increased	Not followed.	
10	54 M	Definite	Balls of feet and toes	1.5	Bilateral	Excessive burning pain	Yes	Yes	No	Yes	Yes	Yes	Flushed; dilated veins	Marked increase†	Condition much worse in right foot.	

* See Table 3.

† See Table 4.

during the attacks. The attacks were usually brought on by exercise, standing and heat, and were accompanied by mild congestion and by pulsations in the veins. At times the attacks were less marked and were not accompanied by definite changes in color. At all times the symptoms were accompanied by sharp increase in surface temperature. Marked pain was usually felt when the temperature of the skin reached about 34°C . (Fig. 1.) The only atypical feature in this case was that, after a period of rest of 5 months, he reported that his condition was markedly ameliorated. I have no evidence that this improvement was complete or permanent.

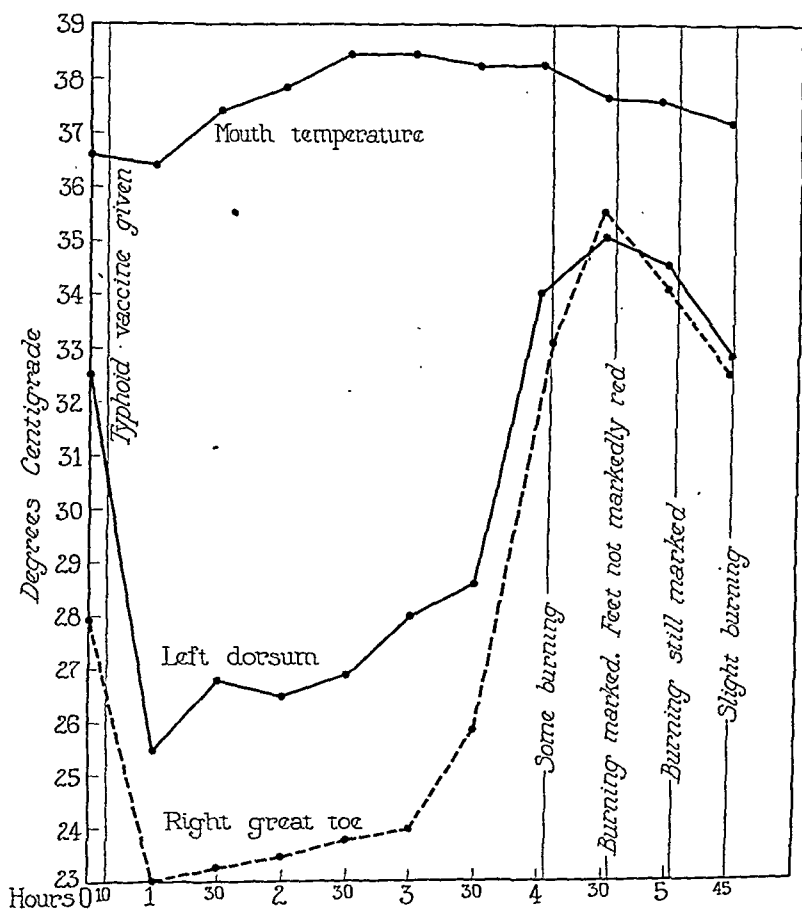


FIG. 1.—(Case 2, Table 2.) Surface temperature of feet in relation to subjective sensation.

CASE 3.—A woman, aged 34 years, with essential hypertension, had attacks of burning pain in the soles of her feet and in the palmar cushions of her fingers and hands. Exercise seemed to be the main exciting factor; hot weather and standing were without definite effects. Likewise, relief was obtained by rest, whereas there was practically no relief from application of cold water and from elevation. During the attacks the involved parts were slightly red and were hot to the touch. The painful areas and increased local heat coincided. Relief from rest was accompanied by a marked drop in local temperature.

CASE 4.—A woman, aged 53 years, with involvement of both hands and feet, had had sensitive feet for many years. This condition had progressed to such a point that when the temperature of the house was more than 70° F. (21° C.) a burning pain developed, accompanied by local congestion and redness of both feet, and associated with a sharp rise in local temperature. She had also noted, within the three months before her registration at the clinic, a similar condition in the hands. The distress was not brought on by standing, but by a moderate amount of exercise, and increase in environmental temperature. Associated with this condition was mild neurosis and nervous exhaustion. The patient was not traced and the subsequent course is unknown.

CASE 5.—A woman, aged 35 years, following a miscarriage 3 years before admission to the clinic, had noted burning and increased heat in the portions of the feet which bear pressure. There were two types of pain—diffuse, superficial burning, and, with further aggravation from exercise, deep, burning pain. There was also increased local heat, mild redness and dilatation of the veins. The hands were also involved to a less degree. There was no sweating during the attacks. The effects of exercise on the surface temperature of the feet are shown in Table 3. Between attacks,

TABLE 3.—EFFECTS OF EXERCISE ON SURFACE TEMPERATURE (DEGREES C.) OF THE FEET.*

Time.	Left foot.		Right foot.		Comment.
	Plantar surface, second toe.	Dorsum.	Plantar surface, second toe.	Dorsum.	
10:45 A.M.	28.5	31.4	31.3	31.7	Feet cool and comfortable; no exercise.
11:30 A.M.	25.8	30.1	29.3	30.6	At rest; no symptoms.
12:00 NOON	25.1	29.5	28.5	30.0	At rest; no symptoms.
3:00 P.M.	35.5	35.5	35.9	35.9	Patient walked 13 blocks; feet dry and hot; burning.
4:00 P.M.	34.9	35.5	35.3	35.1	At rest; no change in symptoms.
5:00 P.M.	33.2	34.1	34.3	34.2	At rest; burning practically disappeared.

* Detail concerning Case 5 of Table 2.

with rest, a difference of 2.8° C. was noted in the surface temperature of the plantar surfaces of the toes of the two feet. Following a brisk walk of thirteen blocks the feet were dry, hot and burning, and the temperature of the left and of the right foot increased to 35.5° and 35.9° C., respectively. With 2 hours' rest the temperature of the left foot had dropped 2.3° and that of the right foot 1.7°, and the burning distress had practically disappeared.

Studies of the effect of posture on the surface temperature disclosed that short periods of elevation produced a decrease of 1° to 2° C. in surface temperature but did not give complete relief. It was found that periods of 30 minutes to an hour were necessary for the temperature to decrease to a point at which burning would disappear. Perception of pain was present when the cutaneous temperature was approximately 33° C.

CASE 6.—To a man, aged 55 years, barometric changes and exercise were the chief factors in producing the burning distress in the feet, whereas rest was the main measure of relief. The effect of atmospheric temperature was not decisive. It seemed necessary to include this case in our series, for during the attacks the surface temperature was as high as 36° C. With a short period of rest the temperature would subside, and the attack was ended. It is possible that some degree of paresthesia, or of progressive,

localized arteriosclerosis may have been present, for subsequent reports from this patient revealed that four years later the condition had largely subsided, and that the feet were giving very little trouble. This case and Case 3 should perhaps be designated as atypical examples of erythromelalgia.

CASE 7.—A man, aged 62 years, 12 years before his admission here, had had his feet "frozen." Following this, he had noticed burning and other paresthetic sensations in the areas of both feet that were subjected to pressure. The abnormal feature was the tendency of the distress to be more or less continuous; the congestion and redness were not pronounced. The aggravating effect of heat, exercise and standing were definite, and relief with elevation, cold and rest was decisive. During the periods of excessive pain the surface temperature of the feet was markedly increased, and it was found that it paralleled the burning sensation. The temperature at which pain appeared was about 33°C . The feet were comfortable at reasonable temperatures below 30°C . It was felt that probably some paresthesia was present in this case. Changes were not demonstrable in the peripheral arteries. Treatment was without avail.

CASE 8.—A man, aged 54 years, 10 years before his registration here, had noted that after he had been on his feet during the day, or had been exposed to heat or exercise, there was hyperhidrosis and there were blisters on the soles of the feet. In the summer of the following year severe burning pain of the soles of the feet developed, and as it progressed involved the lower parts of the legs. The condition was bilateral and symmetric. Aggravation and relief under certain circumstances were typical. The parts were congested during the attacks. The surface temperature was 35°C . during the night, in a warm room, when his feet were covered with bedclothes, at which time he complained bitterly of the pain. During the time he was free from the distress the temperature of the feet was about 25°C . Roentgenograms of the vessels disclosed some calcification of the arteries of the legs, but normal pulsations were present. Cinchophen, contrast baths and enforced periods of rest were prescribed for him. He was observed a number of times, and the condition gradually disappeared in 2 years. It is questionable whether medical measures had any effect on this.

CASE 9.—A woman, aged 78 years, apparently in good general health, for 4 years had had attacks of burning pain in the soles of the feet. She had also noticed small erythematous areas on the soles. These local areas were extremely hot to touch during the attacks. The condition was bilateral, and was brought on by hot weather, walking and standing; relief was obtained by elevation, application of cold and rest. There was no evidence of disease of the arteries of the feet. Roentgenologic examination gave evidence of slight rarefaction and osteoporosis of the bones of both feet. During the periods of distress the surface temperature was sharply increased, but records of exact temperature were not obtained. During the time when she was in comfort the feet were cool to the touch. The condition progressed to a point of almost complete disability. It was felt that the diagnosis of erythromelalgia was justified in this case, but there was also some generalized arteriosclerosis without occlusion, probably compatible with her age. Contrast baths, cinchophen and rest gave slight relief. Her case was not followed.

CASE 10.—A man, aged 54 years, 18 months before admission here, without antecedent disturbances in health, noticed burning pain in both feet, more marked in the right. This difficulty was first noticed in the summer and was especially severe when the patient was playing golf. There had been progressive increase in the severity of the condition. Heat and exercise produced the pain, and rest, cold and elevation relieved it. He described the distress as a deep, burning pain localized on the plantar and dorsal

surfaces of the anterior part of the arch and of the toes. During the attacks the surface temperature was high in the painful portions, and there was marked congestion and dilatation of the veins. Of particular interest were the occasional periods of refractiveness to stimulation, which lasted 7 to 10 days following a severe attack. He could exercise freely during these periods of freedom, without pain. Changes were not demonstrated in the peripheral arteries. Observations during the attack (Table 4) disclosed marked congestion of the right foot, and that surface temperatures in the affected portions ranged from 35° to 36° C. There were hyperesthesia and mild sweating. The pain was intense and localized deep in the foot. Oscillometric tracings disclosed marked increase in amplitude of pulsations of arteries (Fig. 2). The left foot reacted to a temperature of 34.4° C., but was less congested, and pain was present only in the first toe. The right foot was elevated; relief of pain followed, and the surface temperatures and pain decreased in parallel degree. When the surface temperature of the right foot dropped below 33° C. (not shown in table) pain almost ceased. The man was of a hypersensitive type.

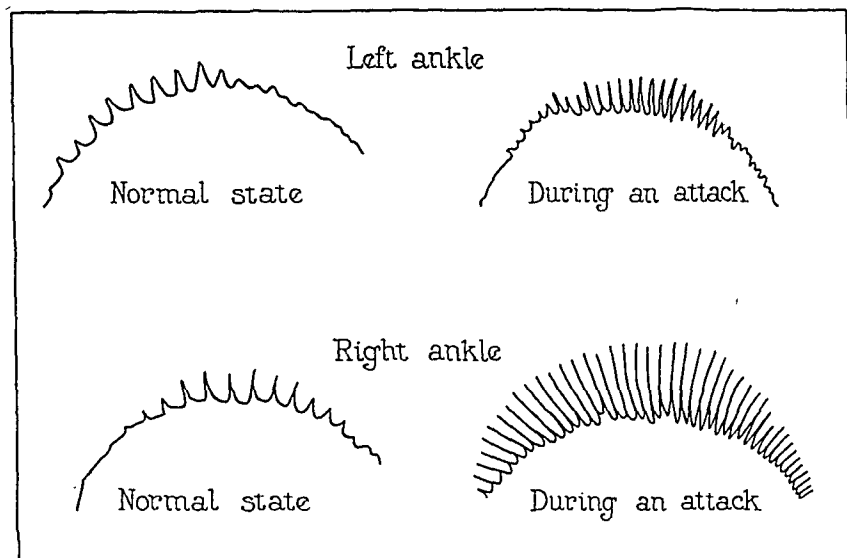


FIG. 2—(Case 10, Table 2.) Oscillometric tracings to demonstrate difference of pulsations in normal state and during attack.

The rate of elimination of heat in the right foot, as measured in the foot calorimeter, during normal periods, was 33 small calories for each minute for the entire foot, or 0.32 small calories for each square inch for each minute (normal range, 0.46 to 1.15). During an attack the loss of heat for the entire foot was 205 calories, or 2.01 calories for each unit area (Fig. 3). This measurement of transference of heat is an indirect measure for volume flow of blood in a unit of time, and the figures obtained in this case indicate a huge increase of more than 600 per cent in flow of blood during the period of vasodilatation.

The studies on the concentration of oxygen in the venous blood of the right foot before and during the attack were also instructive. With the surface temperature measuring 31° C., and no subjective symptoms, the concentration of oxygen was 57 per cent, a normal value. During the phase of active vasodilatation, when the cutaneous temperature was 35.3° C., the concentration of oxygen was 83 per cent. This indicates blood with oxygen content approaching that of arterial blood (94 to 96 per cent). This gives further evidence of the high degree of dilatation of the arterioles.

TABLE 4.—SURFACE TEMPERATURES (DEGREES C.) OF FEET DURING ATTACK.*

Time, A.M.	Right foot.		Left foot.		Comment.
	Dorsum.	Plantar surface, anterior arch.	Dorsum.	Plantar surface, anterior arch.	
	32.2	31.6	31.2	31.4	Patient at rest; comfortable; no pain.
	32.4	31.4	31.2	31.6	Control period.
9:20	..	34.2	Right foot flushed, graded 1; veins prominent; burning distress just perceptible.
9:25	..	34.9	Foot covered and at level of body.
9:32	..	36.5	Subjective feeling of heat and burning pain; increase of subjective burning; veins dilated.
9:45	..	36.7	Foot felt as if on fire; pain more severe.
9:50	..	36.8	Throbbing burning pain; face flushed; mild tachycardia; rate 100.
9:55	..	36.4	Foot hanging down; violent burning pain.
10:00	..	36.1	..	34.4	Right foot elevated; slight subjective relief; left foot in horizontal position.
10:05	..	35.9	Gradual relief of pain and burning.
10:20	..	35.6	..	35.3	Mild residual burning; burning in left foot.
10:25	..	35.5	..	35.5	Burning slight; moderate pain in left foot.
10:30	..	35.4	Residual burning in right first toe.

* Details concerning Case 10 of Table 2.

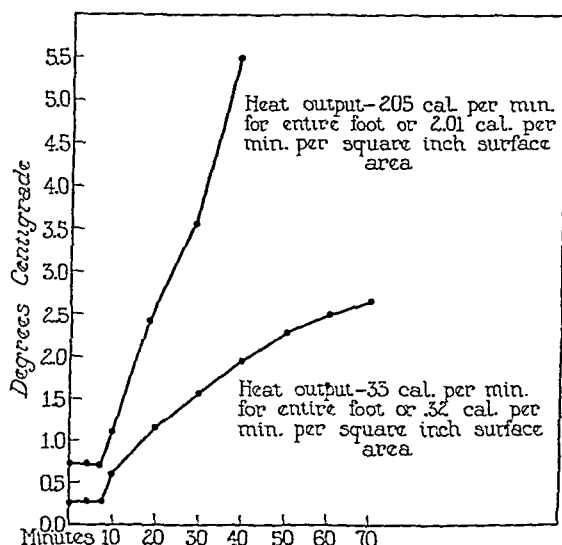


FIG. 3.—(Case 10, Table 2.) Increased limitation of heat during an attack of pain, with great vasodilatation.

Study of Group 2: Unilateral Disturbance in Vasodilatation. This group was composed of 3 cases of disturbance in vasodilatation, 2 of which were typical of erythromelalgia, except that the condition was unilateral. (Table 5.)

TABLE 5.—CASES OF UNILATERAL DISTURBANCE OF VASODILATATION OF THE EXTREMITIES SEEN AT THE MAYO CLINIC.

Case.	Age in years and sex.	Parts affected.	Duration of complaint, years.	Character of attacks.	Subjective symptoms.	Exciting factor.	Factor giving relief.	Color of parts during attacks.	Swelling of parts.	Surface temperature of affected area during attacks.	Pulsation of blood-vessels.	Treatment.	Results; subsequent history.
11 . .	46 M	Right foot	20	Definite	Burning pain	Spontaneous	Elevation and walking	Unchanged	None	Right foot 30.1° C.; left foot 27.6° C.	Normal	Contrast baths	Not followed.
12 . .	48 M	Right foot; anterior arch	1	Indefinite	Burning pain	Hot weather and exercise	Elevation	Red at times	None	Right foot almost 1° higher than left	Normal	Rest and cold foot baths	Pain 6 months later.
13 . .	48 M	Palmar surfaces of fingers of left hand and 3.5 years later left foot	2.5	Indefinite	Burning throbbing pain	Hot weather and exercise	Elevation, cold water and partial relief with rest	Purplish red; local sweating	Questionable	Right first finger 27.9° C.; left first finger 34.2° C.	Normal	Radium locally	Complete relief in 3 months; returned 3.5 years later with similar condition of left foot.

CASE 11.—A man, aged 46 years, had attacks that appeared spontaneously during the night, with relief on walking. Thus, the factors of excitement and relief were not typical. However, the patient was included in this series because the symptoms and increase in surface temperature were closely parallel. Apparently the condition was primary, for no causative factors were found.

CASE 12.—A man, aged 48 years, had a characteristic case, except that the symptoms were limited to the right foot. The surface temperatures of the right and of the left foot during periods of rest and during periods of exercise (Fig. 4) show clearly the unilateral nature of the disorder, and that the threshold for burning was approximately 33.5°C . With a drop in

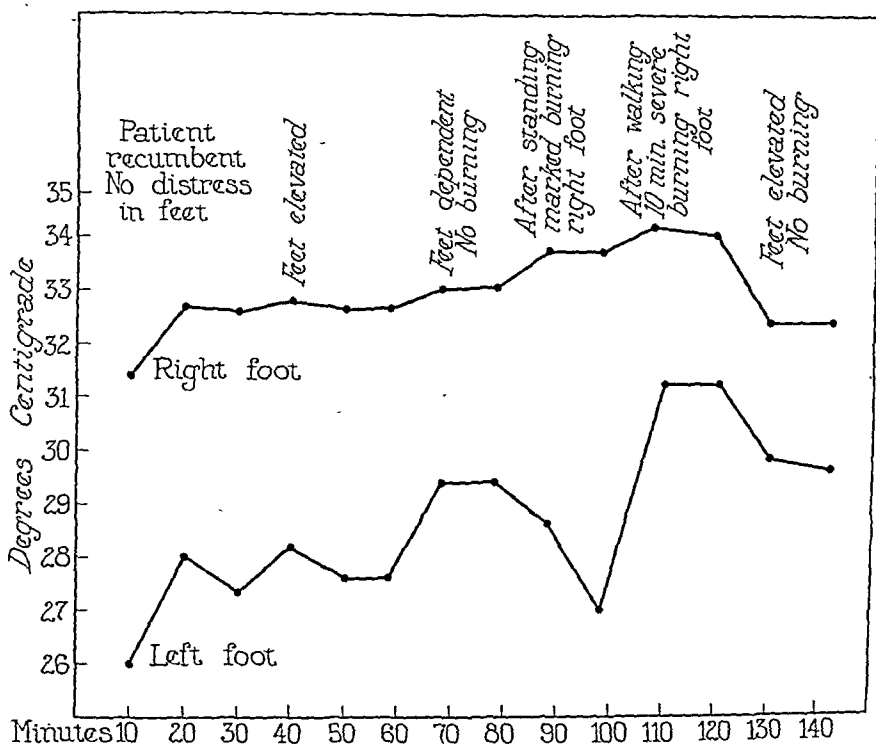


FIG. 4.—(Case 12, Table 5.) Surface temperature of feet in a case of unilateral disturbance of vasodilatation.

temperature of approximately 1°C ., the burning was relieved. The response to exercise of surface temperature of the left foot was approximately that obtained in a normal person.

CASE 13.—A farmer, aged 48 years, gave a history of having had a burning sensation in the palmar surfaces of the fingers of the left hand for $2\frac{1}{2}$ years. Objectively, during the attacks the finger pads, and the regions at the bases of the fingers, became intensely red, swollen and congested, with marked increase in the surface temperature. These episodes were brought on by exercise and by hot weather; relief was obtained by elevation, application of cold and rest. The surface temperatures of the palmar surface of the left first finger during the painful attack reached 34.2°C ., but in the corresponding region on the right, or unaffected side, the temperature was

27.9° C (Table 6). Hyperhidrosis and hyperesthesia of the affected parts were present during attacks. The condition at times became very distressing and had progressed until it had caused almost complete dis-

TABLE 6.—TEMPERATURE (DEGREES C.) OF RIGHT AND LEFT HANDS IN DISTURBANCE OF VASODILATATION OF LEFT HAND.*

Time, P.M.	Left palmar surface.		Right palmar surface.		Comment.
	First finger.	Third finger.	First finger.	Third finger.	
3:30	34.2	34.1	27.9	29.9	Patient at rest; burning pain in left hand.
4:10	32.9	33.4	26.3	28.7	
4:45	32.6	32.7	24.3	27.7	
5:30	30.9	30.8	22.4	25.7	

* Detail concerning Case 13 of Table 5.

ability. Nothing was found in the examination to indicate any predisposing factor or a primary disease. Six months following local application of radium the patient obtained complete relief. He returned 3½ years later, with a similar condition in the left foot (data not included in Table 5).

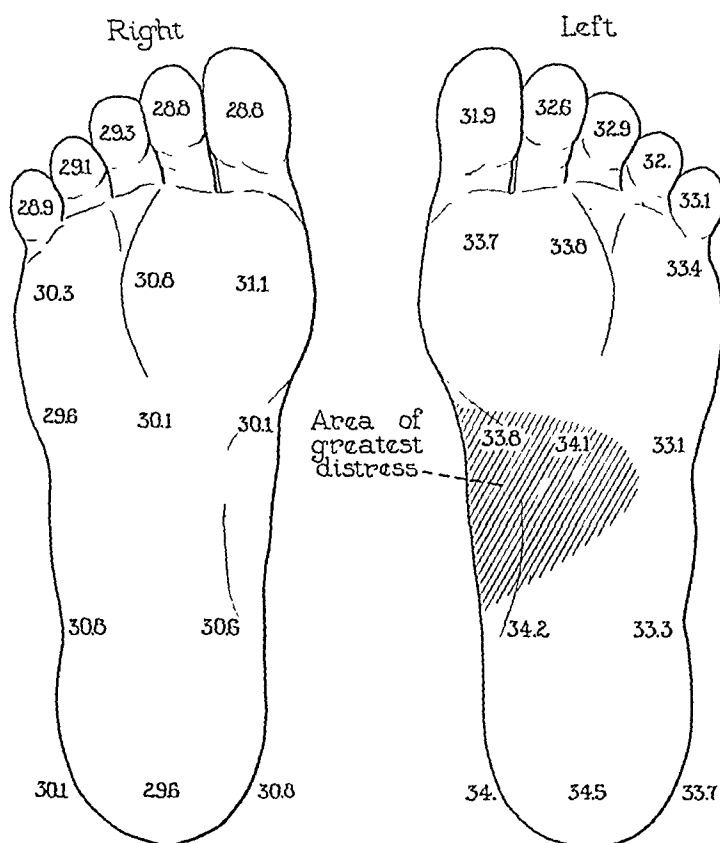


FIG. 5.—(Case 13, Table 5.) Shaded portion indicates painful area. Numerals indicate surface temperature which is evidence of unilateral nature of the disturbance.

This had developed in the preceding year. The attacks were excited by exercise and hot weather, and relief was obtained by elevation and application of cold. The areas of vasodilatation are shown in Fig. 5. Slight

symptoms were present also in the right foot, but they were very mild and practically unnoticed by the patient, unless he was specifically questioned. It will be noted from this figure that the area of greatest distress corresponded rather closely with the greatest increase in surface temperature. Both feet were somewhat congested, the veins were dilated, and if exercise was persisted in the entire foot participated in the "vascular storm." During an attack the output of heat was 42 calories for each minute for the entire foot, whereas elimination of heat from the left foot was exactly half of this. An interesting feature in this case was the evidence of possible early polycythemia vera. The blood volume was 103 cc. for each kilogram of body weight; the percentage of cells by the hematocrit method was 57; the concentration of hemoglobin was 117 per cent, and erythrocytes numbered 5,630,000 per c.mm. The spleen was not palpable, but the appearance of the man's face and mucous membranes suggested early polycythemia vera. Diagnosis cannot be made until time has elapsed. Radium was applied locally, the results of which are not known to date.

There is some question as to whether the 3 cases in this group should be considered to be examples of erythromelalgia. If the condition had been definitely bilateral doubt would not have been raised. That it was unilateral throws grave doubt on the correctness of diagnosing these conditions as erythromelalgia. In my opinion, it would be necessary for complete follow-up study of these patients to be carried out to make certain that no underlying primary disease was present, particularly polycythemia vera, since unilateral vasodilating disturbances have been fairly common in this condition.

General Comment. It is apparent from this study that the syndrome described by Mitchell represents one of the conditions that is most rarely found in clinical medicine. Statistics at The Mayo Clinic indicate that the incidence is approximately 1 case in every 200 cases of peripheral vascular disease, and that the yearly incidence is 1 to 40,000 cases for the total number of patients registered.

It is important to separate from the group of cases of erythromelalgia those cases in which there is burning pain in the hands and feet, secondary to other diseases. The hot, burning disturbances of acral portions, observed in polycythemia vera, may especially be mentioned. This interesting phenomenon of vasodilatation is frequently a precursor, or early symptom, of polycythemia vera, and at times is the only condition of which complaint is made. Similarly, vasodilatation is present in some cases of peripheral neuritis, especially those due to the toxic effects of the heavy metals, such as thallium, mercury and arsenic. Cases of gout are at times confusing; response to rest, heat and exercise make it possible to distinguish erythromelalgia from other conditions.

Greater difficulty is encountered in older subjects who give some evidence of peripheral and general arteriosclerosis, and whose major complaints are of burning extremities. These conditions frequently are bilateral, and symptomatically they conform, in some degree,

to erythromelalgia. The great majority of these cases are examples of paresthesia of central origin. The essential point to determine is whether the subjective symptom of burning is associated with increase in heat of the affected part. I have found that some vasodilatation is often present. It is essential to learn, then, if the increase in surface temperature attains a level of 33° to 36° C., and if this increase, and the return to normal after it, parallel the pregression and regression of the subjective distress. Usually the other paresthetic symptoms, and the factors of atypical relief and aggravation, indicate clearly their paresthetic nature. There is a larger group of older subjects who have burning distress in the feet but who do not give evidence of vasodilatation. A definite point in eliminating this group from consideration as examples of erythromelalgia is the statement by the patient: "While my feet are cold, they burn." This is easily corroborated by determinations of surface temperature made in the periods of distress. Dissociation of burning and surface temperatures is the rule. This condition is designated as burning paresthesia. It usually occurs in older subjects, who give evidence of cerebral and local arteriosclerosis, and after hemiplegia of hemorrhagic or thrombotic origin. Definite information on this point can be obtained by spinal anesthesia; with complete analgesia of the affected parts the burning distress may still persist.

The perception of pain in relation to surface temperature is of interest. This varies within a fairly narrow range, but the increase in temperature does not furnish the sole explanation of the subjective distress. Sensitivity of the patient must play a large part, and intermittency of the periods of vasodilatation is important. Patients who have undergone lumbar ganglionectomy often have surface temperatures of the feet of 33° to 34° C., but subjective burning is rarely present. One patient, following cervicothoracic ganglionectomy for arthritis, had subjective burning in the hands, and relief was obtained by elevation. This condition disappeared in 8 or 10 days. The high surface temperature is fairly constant, and perception of it is dulled. If fluctuations of cutaneous temperature are rapid, and extend over a range as wide as 8° to 10° C., I believe distress would be noted subjectively. If this occurred in a hypersensitive person probably severe pain would be the complaint. An additional unknown fault of the nervous system may be necessary to produce the syndrome.

Bilateral distribution of the objective and subjective manifestations of erythromelalgia is most essential to its identification. However, complete symmetry may be lacking. It was observed in practically all of my cases that in one extremity there was a greater amount of vasodilatation and subjective distress than in the other. This is well shown in Case 10 (Table 2). The complaint was largely of a unilateral condition, but it was found that the dis-

turbance was bilateral, aggravated in the right foot. This variation in the grade of vasodilatation was fairly frequent. There remained 3 patients in whom the disturbance of vasodilatation was distinctly unilateral, both as regards objective evidence and subjective complaints. These cases could not be accepted as examples of erythromelalgia. I am of the opinion that this disturbance of vasodilatation may be a precursory symptom of some other disease.

It is evident that patients who complain of sensations of burning in the extremities offer considerable trouble in diagnosis. Satisfactory nomenclature is lacking. However, I believe accurate studies of surface temperature in relation to subjective distress allow primary separation into two groups: those with and those without local vasodilatation.

This distinction is fundamental: if increased vasodilatation is present, and parallels the degree of pain or distress, and is bilateral and intermittent, I believe the diagnosis of erythromelalgia is warranted, provided primary or associated disease is not present. If these features are present relief by application of cold or by elevation and aggravation by exercise or heat seems necessarily a corollary.

Of special interest is the refractory state that was observed in Case 10 (Table 2). Following a fairly severe attack induced by exercise, for 6 to 10 days an equal or greater amount of exercise would produce slight, if any, vasodilatation. Then, if a period of rest of a few days was given exercise would excite a severe attack. A systemic reaction, consisting of tachycardia and slight flushing of the face, with a sensation of heat, was observed during a severe local reaction in the feet. This observation is most unusual, and may throw some light on the etiologic mechanism of erythromelalgia, suggesting a possible chemical or hormonal agent as a basis for the vasodilatation. An analogy to this is observed in certain cases of cold allergy with systemic reactions.

Since excess volume of flow of blood is the basis of the symptoms in erythromelalgia, gangrene or trophic changes should not ensue. The cases reported in the literature as erythromelalgia with gangrene, I am convinced must be erroneous. They probably represent either cases of thromboangiitis obliterans, with the usual rubor or cases of arteriosclerotic disease, with burning paresthesia.

The treatment of erythromelalgia is still unsatisfactory. Two of the cases which I have seen recently responded well to application of radium locally, and I believe this should be tried in all cases. However, these patients have not been observed for a sufficiently long period to allow me to be certain of the lasting effect of this treatment. In the cases of long standing some degree of mental deterioration may develop, due largely, I believe, to the unending annoyance and distress incident to the disease.

Summary and Conclusions. Erythromelalgia, first described by Weir Mitchell, is a vasomotor disturbance of unknown etiology and is an extremely rare disease. The term erythromelalgia is not entirely accurate, since redness and pain in the extremities are common to several vascular diseases of diverse types. In erythromelalgia attacks of local vasodilatation, with increased local heat and pain, constitute the basic disturbance.

Four fundamental criteria are essential to diagnosis of the disease: (1) Bilateral burning pain in the extremities; (2) sharp increase of local heat in the affected parts, but redness, flushing or congestion may vary in degree; (3) production and aggravation of the distress by heat and exercise, and (4) relief by rest, cold and elevation.

During the attacks the temperature of the affected parts should be found to reach or exceed 33° or 34° C. and pain usually becomes evident when this temperature is reached or exceeded. Augmentation in arterial pulsation and in the rate of loss of heat give further evidence of the high degree of dilatation of arteries.

Certain methods of study to distinguish between the different conditions in which burning extremities occur are outlined.

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THE BLOOD PRESSURE IN THE ARTERIES OF THE EXTREMITIES IN NORMAL SUBJECTS AND IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE.

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IN the study of the abnormal physiologic changes resulting from vascular diseases of the extremity the blood pressure is an important factor, for in any hydrodynamic system, flow is a function of pressure and cross-sectional area. It is apparent that the frequent involvement of the vessels of the lower extremities makes it desir-

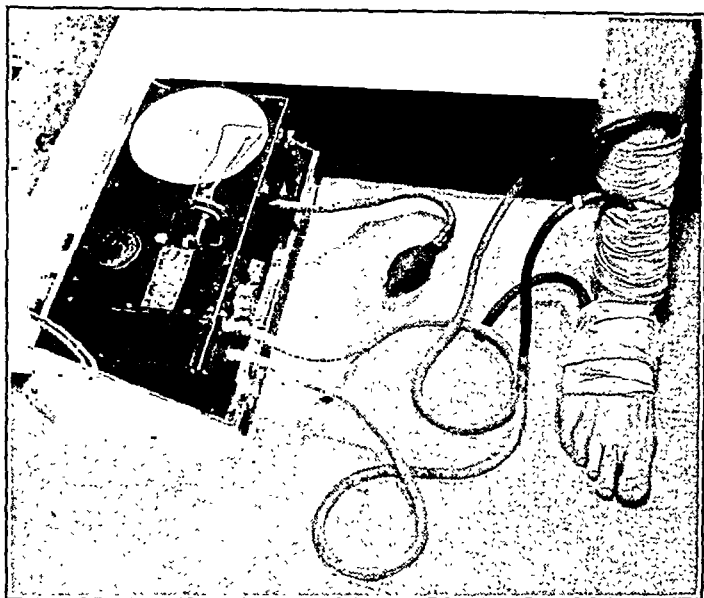


FIG. 1.—The cuffs for recording the blood pressure in the dorsalis pedis and posterior tibial arteries applied to the limb and attached to the sphygmomanometer. The lowest cuff is for the dorsalis pedis, the middle one is for the posterior tibial and the upper one is a "shut off" cuff.

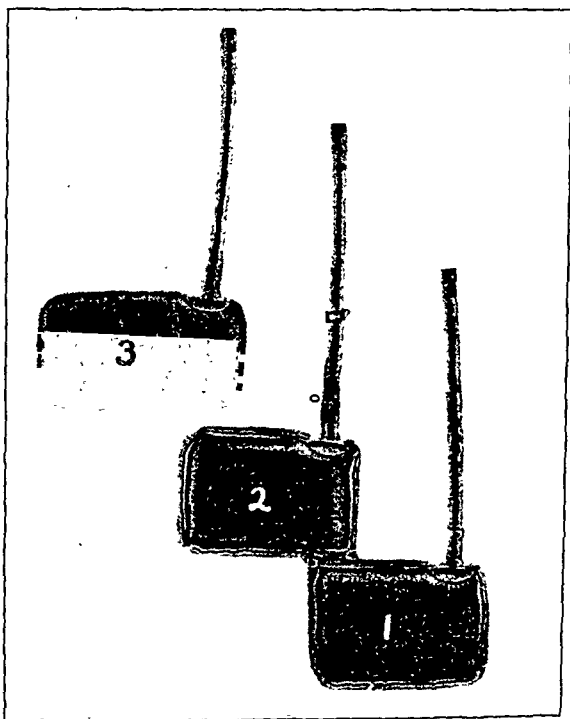


FIG. 2.—The arrangement of the special cuffs: No. 1, dorsalis pedis; No. 2, posterior tibial; No. 3, "shut off." Although No. 1 and No. 2 are attached there is no communication between them.

able to obtain data on the pressure changes in this location but no apparatus has heretofore been available for such measurements. With the development of a reliable recording sphygmomanometer* it was thought to be possible, by using special cuffs, to obtain the pressure in the dorsalis pedis and posterior tibial arteries (Fig. 1). These cuffs were made† (Fig. 2) and were found to give a satisfactory record of the blood pressure in these vessels. It was then decided to study, not only the changes with arterial disease, but also the alterations in pressure brought about by changes in posture in normal adults.

It is well known that in the presence of occlusive vascular disease elevation of the extremity results in pallor and ischemia, while dependency of the structure causes rubor and cyanosis and this has been assumed to be a hydrostatic effect. In order to determine the changes in arterial pressure with alteration in position, 16 normal adults were studied. After a period of rest in the horizontal position, the pressure in the brachial, dorsalis pedis and posterior tibial arteries was determined. That of the latter 2 vessels was then recorded, first in elevation at an angle of 45 degrees and then in dependency with the limb hanging over the edge of the table. The results are shown in Table 1 from which it is seen that the average pressure in the brachial artery is midway between the pressure in the posterior tibial and dorsalis pedis, that of the former being consistently higher, while the latter is at a lower level. This is shown in Fig. 3. The effect of alteration in position may also be noted from this table and is shown in Fig. 4. If the lower extremity is elevated at an angle of 45 degrees the average fall in pressure in the posterior tibial artery is found to be 46 mm. Hg. The average height of elevation above the horizontal was 660 mm. and computation of the hydrostatic effect shows a theoretical change of 51.3 mm. Hg., which gives a difference from the recorded change of 5.3 mm. Hg. The dependency of the limb at an angle of 90 degrees caused an average rise of pressure in the posterior tibial artery of 28 mm. Hg. The average amount of depression below the horizontal was 390 mm. which would give a hydrostatic effect of 30.3 mm. Hg. and hence a difference of 2.3 mm. Hg. from the recorded result. A typical record of the change in pressure with a shift in position is shown in Fig. 5.

The same correlation between the theoretical and actual results of alteration in position is found in the case of the dorsalis pedis artery. In this vessel an average elevation of 680 mm. gives a fall in pressure of 39 mm. Hg., while the calculated hydrostatic effect is 52 mm. Hg., and an average depression of 410 mm. gives a rise of pressure of 37 mm. Hg. with a calculated change of 32 mm. Hg.

* Tycos recording sphygmomanometer.

† We are indebted to Mr. Samuel Amdursky of the Taylor Instrument Companies for his assistance in obtaining the desired apparatus.

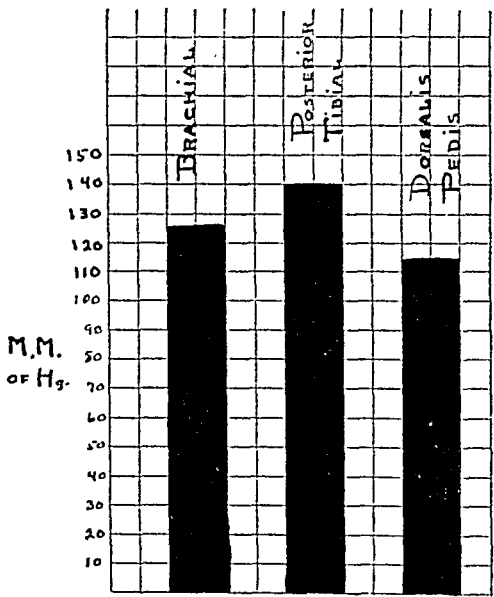


FIG. 3.—The normal relation of the systolic blood pressure in the horizontal position at rest in the brachial, posterior tibial and dorsalis pedis arteries.

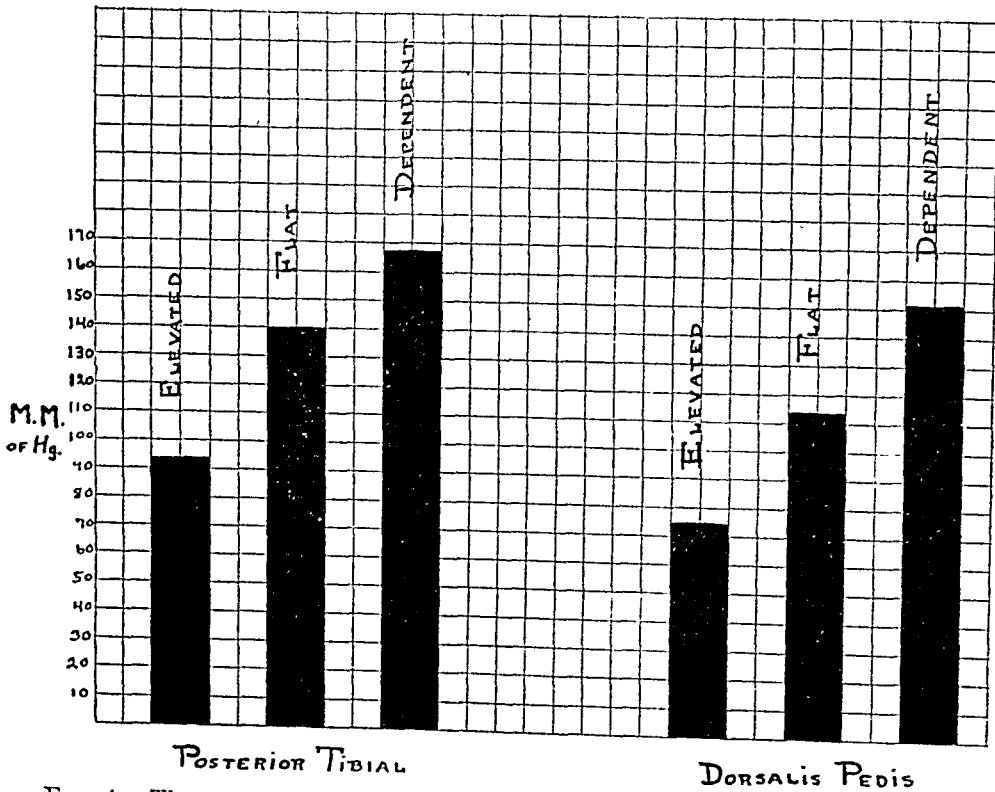


FIG. 4.—The average change in systolic blood pressure due to alteration in position of the limb.

The results recorded with the dorsalis pedis artery are probably not entirely accurate because the weak character of its pulse, particularly with the limb elevated, made interpretation of the records difficult.

If simultaneous readings are taken on the pressure in the brachial and posterior tibial arteries it is noticed that with elevation of the limb and consequent fall in pressure in the vessels of the extremity there was a slight rise in the pressure of the brachial artery. It is possible that the elevation of the limb reduced the volume flow through the extremity and hence increased the blood volume in the general circulation. The converse of this effect is noted with depression of the extremity.

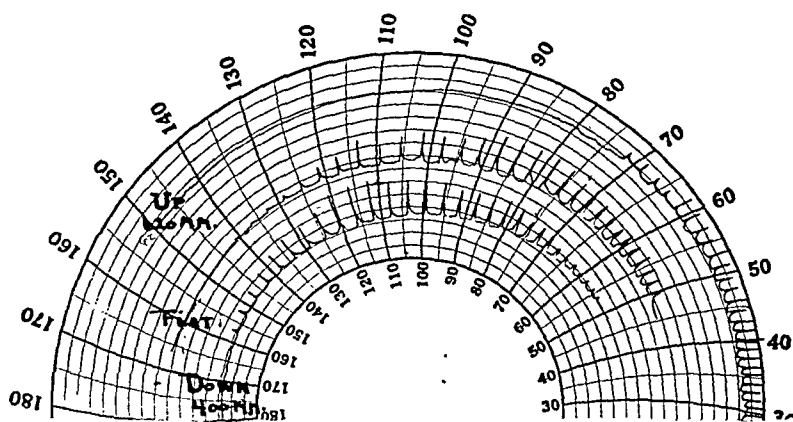


FIG. 5.—A typical chart of the effect on the blood pressure and amplitude of the pulse wave in the posterior tibial artery of elevating and depressing the limb.

The instrument used has the advantage of giving not only a permanent record of the blood pressure in the vessel being studied but also gives a chart of the strength of the arterial pulsation. This latter effect is the same as the oscillometric determination with the Pachon instrument and is of equal importance. When applied to the dorsalis pedis and posterior tibial arteries it serves to give an index of the caliber of these vessels. In normal subjects it was observed that if the pulsation in one of these vessels was vigorous that in the other was often weak. It most frequently occurred that the posterior tibial had the stronger pulsation and occasionally it was found to be impossible to record the pulse in the dorsalis pedis artery. It appears that a reciprocal relation exists between these vessels.

It was hoped that by means of a sensitive instrument, pressure could be recorded in the posterior tibial and dorsalis pedis arteries even in the absence of a perceptible pulse. It is well known that blood flow occurs in a vessel in which no pulse can be detected. However, this was found to be impossible and no record could be

obtained if the perceptible pulsation of the peripheral vessels was absent. On the other hand, it was found that by using the arm cuff applied to the leg a record of the intravascular pressure and amplitude of the pulse could be recorded for the larger vessels. The study of the force of the pulse wave in these arteries gives a record of the oscillometric effect and may be used to determine the level and degree of involvement in cases of thrombotic or sclerotic occlusion. An illustration of this is shown in Fig. 6 which is a tracing from a case of diabetic endarteritis with a pregangrenous lesion. It will be seen that the force of the pulse just above the knee (popliteal artery) is good, while just below the knee (tibial and peroneal arteries) it is nearly absent. This shows that the level of

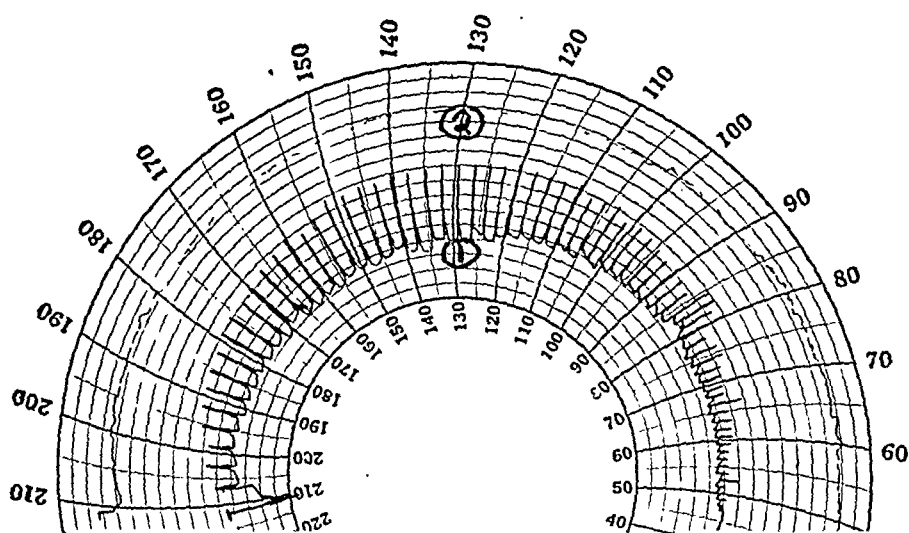


FIG. 6.—Diabetic endarteritis with abrupt arterial occlusion. The popliteal artery (1) just above the knee has a strong pulse while there is no pulse; (2) 3 inches lower at the level of the tibial tubercle. Subsequent dissection showed the obstruction at the bifurcation of the popliteal artery into its posterior tibial and peroneal branches.

occlusion is near the bifurcation of the popliteal artery and that the vessel above this point is not seriously involved. Subsequent dissection confirmed this finding. The use of the instrument to obtain a record of the character and amplitude of the pulse in patients with arterial disease of the extremities gives concrete information that is of value in deciding upon the therapy to be used. Various types of involvement are found varying from gradual progressive occlusion (Fig. 7) down the leg to sudden, sharp level of thrombotic obliteration.

Discussion. The data presented show that a change in posture of the lower extremities materially alters the blood pressure in the arteries of the limb. Change of position also influences the strength of the pulsation of the vessel. When the leg is in the dependent position, the systolic and diastolic pressures increase and the pulsa-

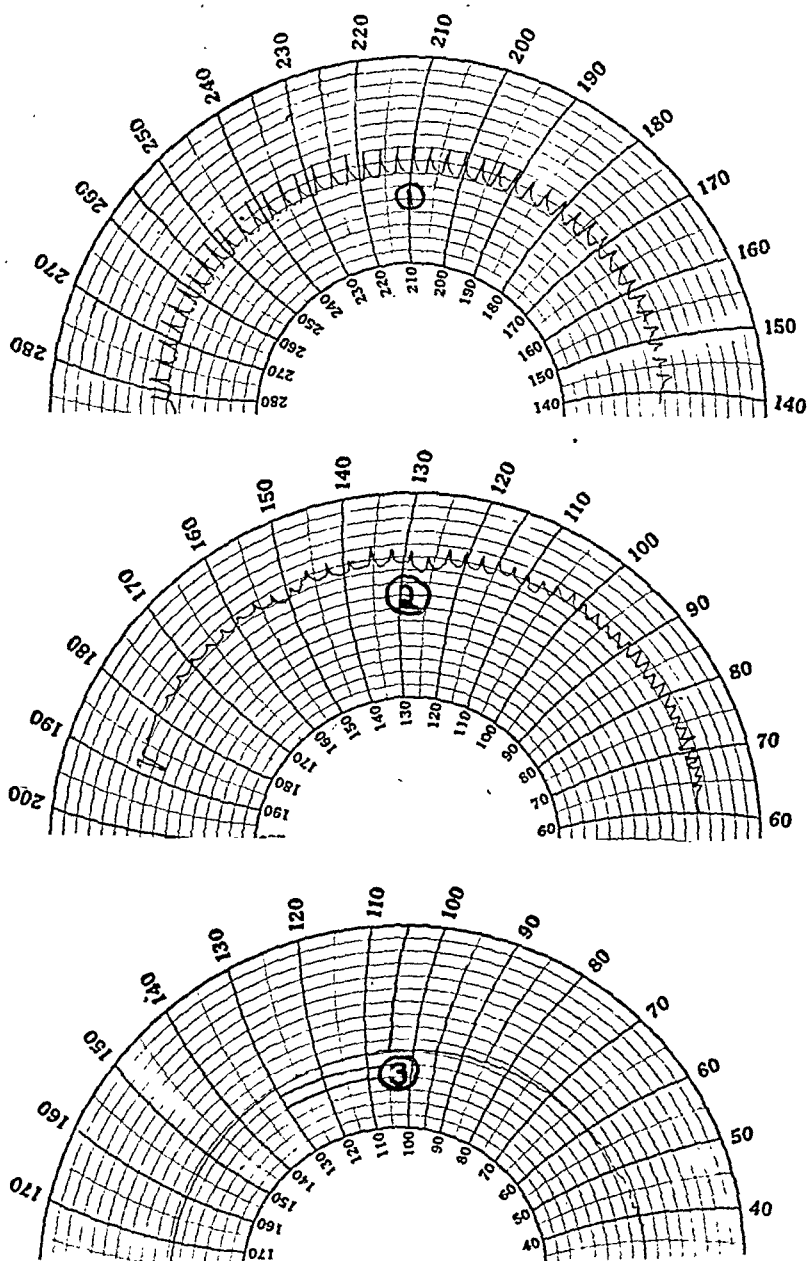


FIG. 7.—Gradual arterial occlusion from arteriosclerosis: 1, shows a good pulse below the knee; 2, shows a diminished pulse at midcalf, and 3, shows an absent pulse at the ankle. The posterior tibial and dorsalis pedis pulses were imperceptible.

tion is maximal. Elevation of the limb gives the opposite effect, namely to decrease the blood pressure and diminish the force of the pulse. This result gives a mechanical explanation of the phenomena observed with change in position of a limb afflicted with severe arterial disease. Under such conditions, an important part of the physical examination is the observation of the effect of posture on the circulation of the part. It is found that elevation results in blanching, pallor and even a cadaveric appearance. This ischemia is produced at a definite angle in each individual depending upon the amount of arterial involvement and Buerger² has defined this as the angle of vascular sufficiency. Samuels⁷ has shown that motion of the toes accelerates this phenomena and may in addition produce symptoms resembling intermittent claudication. Matas⁴ has made use of the circulatory changes accompanying shift of position to evaluate the level of efficiency of the collateral circulation. It is obvious that if the blood pressure and force of the pulse are diminished in normal subjects by elevating the limb, then under conditions of impaired circulation there is apt to be complete incompetence in this position and ischemia will result.

The depression of the limb, with its consequent increase in blood pressure and force of the pulse, allows more blood to be forced through the narrowed channels. It has been shown⁵ that in the later stages of obliterate endarteritis the vasomotor control and vasomotor gradient in the lower extremities is obliterated. Thus, there will be no counteracting mechanism for the increased pressure of the hydrostatic effect and cyanosis and rubor will result. Turner, Newton and Haynes⁹ have recently demonstrated an increase in the blood content of the legs held in dependency.

In the management of patients with peripheral vascular insufficiency this effect of position on the circulation should be considered. If the circulation is incompetent the limb should never be elevated except during brief intervals for the purpose of exercise. It would appear to be beneficial slightly to depress the leg thus increasing the intravascular pressure but this should never be done to the extent of causing rubor or cyanosis since edema may result.

Little need be said of the use of the instrument for determining the force of the pulse wave in subjects with vascular disease. This method is exactly similar to oscillometry with the Pachon⁶ instrument and Samuels⁷ has discussed the value of oscillometry in these conditions. Recently Simpson⁸ has compared the Pachon and Tycos machines in a variety of vascular disturbances. We have used the Pachon instrument for a number of years and we feel that with the recording sphygmomanometer, there is not only the advantage of having permanent calibrated records but also that this instrument is more sensitive and gives more reliable readings than does the Pachon. Burdick *et al.*³ have recorded the differences in blood pressure in the arm and leg of normal subjects and have

shown that the femoral pressure is consistently higher than that of the brachial. Our observations show that this difference extends to the posterior tibial artery as well. The explanation of this phenomena is given by Bazett¹ to be the conversion of kinetic energy into stress.

It is expected that the further use of the apparatus described will not only aid in obtaining accurate information about cases of arterial disease but also will serve to advance our knowledge of peripheral vascular physiology.

Summary and Conclusions. 1. The effect of alteration in position of a limb on the blood pressure of the peripheral arteries has been studied. It was found that elevation of the extremity lowered the blood pressure while its depression raised the intravascular pressure. These results correlated with the theoretical hydrostatic change of such a maneuver.

2. In peripheral vascular lesions it is essential to know the condition of the main arteries as well as that of the arteriolar and subpapillary branches. The vasoconstrictor influence upon the latter structures is demonstrated by a skin temperature response to known agents. The state of the main vessels can only be determined by estimation of the perceptible pulse or by oscillometry.

3. In the past the Pachon instrument has been the standard for oscillometric determinations. The Tycos recording sphygmomanometer has the advantage of giving an accurate, permanent calibrated record for this purpose.

4. The use of this instrument with the special cuffs devised is considered desirable to determine not only the condition of the vessels in disease but also to study vascular physiology.

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CORONARY DISEASE IN 100 AUTOPSIED DIABETICS.

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SINCE the discovery of insulin the clinical picture of diabetes has been changing. While in the preinsulin era malnutrition, infection, acidosis and coma were the chief problems and dangers of the diabetic, we now find that vascular disease is playing a greater part, while coma is becoming more and more infrequent. This is well brought out by the statistics of Joslin,¹ in an analysis of 1756 diabetic deaths. It will be noted that since the introduction of insulin the deaths from vascular disease have increased from 28 to 47 per cent. In a more recent series of 42 diabetic deaths reported by Joslin,² in 1928, not a single death was due to coma and about one-half died of vascular diseases.

It is a familiar fact that the peripheral arteries of the diabetic are prone to sclerosis. Attention was drawn to this early, because of the frequency of peripheral gangrene in diabetes and the presence of sclerotic vessels in amputations for gangrene. More recently the clinical detection of peripheral arteriosclerosis has been made even more exact by the use of the Roentgen ray method. Aside from the peripheral arteries, comparatively little attention has been given to changes in other vessels.

Warren and Root³ found in 17 autopsies on diabetics above the age of 40 years 5 cases with no coronary sclerosis, 4 with slight change and 8 with marked coronary disease and myocardial degeneration. Vascular disease apparently was more frequent in the obese. Wilder,⁴ in 58 autopsies at all ages, found 34 per cent showing extensive coronary disease. In 75 per cent of the cases with peripheral gangrene a high degree of coronary sclerosis was noted. Bowen and Koenig⁵ recently published an excellent report on the study of the peripheral arteries in the diabetic by means of the Roentgen ray. Incidentally, they presented a table of 18 cases from a series examined, in 1924, who had died since that time. Of these 18 cases 7 died cardiac deaths, 5 of these presenting the characteristic clinical features of coronary thrombosis.

In the present study the records of 100 diabetics that came to autopsy were analyzed with special reference to the cardiovascular pathology. The coronary arteries were considered as diseased only when there was marked sclerosis with definite narrowing and partial obliteration of the lumen of one or more large branches, for it is this type which has definite clinical significance. The essential data are summarized in Tables 1, 2, 3 and 4 and Chart I.

DISCUSSION OF TABLES. Table 1: In this table the incidence of coronary disease by decades is presented. It is to be noted that whereas the frequency is low in the earlier decades, there is a sharp rise above the age of fifty years. Of 26 autopsies below this age there are but 2 instances of coronary disease, or 7.7 per cent. Of the 74 autopsies above the age of fifty years coronary disease was present in 39 cases, or 52.7 per cent. This high incidence of coronary sclerosis is in fairly close agreement with the above mentioned report of Warren and Root. These observers, in 17 diabetic autopsies above the age of 40 years, found 47 per cent showing extensive coronary disease. Wilder, in 58 autopsies at all ages, found an incidence of 34 per cent, as compared with 41 per cent in the present series of 100 autopsies. Hepburn and Graham⁶ studied the electrocardiograms of 123 clinical cases of diabetes at all ages. Electrocardiographic abnormalities were present in 45.5 per cent, which for the most part were characteristic of coronary disease.

TABLE 1.—CORONARY DISEASE IN DIABETES.

Age.	Autopsies, 100.	Coronary sclerosis.	
		No. of cases, 41.	Per cent, 41.
10 to 20	1	0	0
20 to 30	2	0	0
30 to 40	11	1	9.0
40 to 50	12	1	8.0
50 to 60	27	14	52.0
60 to 70	33	17	52.0
70 to 80	12	6	50.0
80 to 90	2	2	100.0
Above age of 50	74	39	52.7

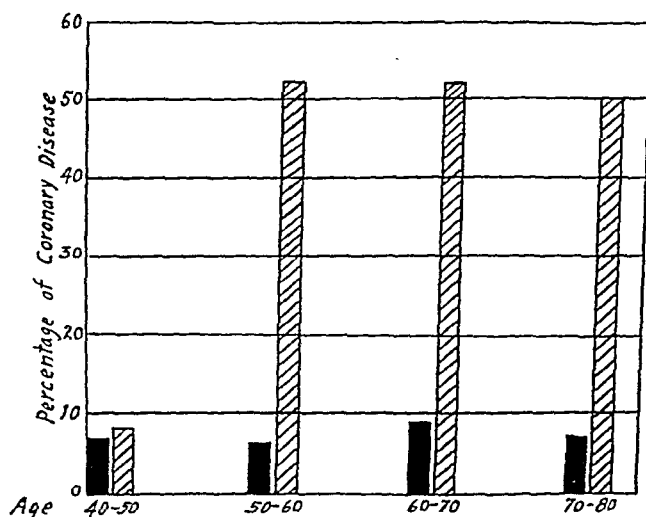


CHART I.—Comparison of the incidence of coronary disease in diabetics and non-diabetics. Shaded columns, diabetics; solid columns, nondiabetics.

Since in any series of autopsies above the age of fifty years coronary disease is not an infrequent finding, it seemed necessary to compare the incidence of coronary sclerosis in autopsies on diabetics with that in general autopsy material. Of 249 consecutive autopsies above the age of fifty years there were 21, or 8.2 per cent, showing extensive coronary sclerosis as compared with 52.7 per cent in the diabetic series of 100 autopsies. The difference in the two groups is thus very striking, indicating that above the age of fifty years the incidence of coronary disease is approximately six and a half times greater in diabetics than in nondiabetics. Chart I shows graphically the comparative frequency of coronary disease in diabetics and nondiabetics by decades.

Table 2: This table shows the distribution of the cases of coronary disease according to sex. It will be noted that there is a preponderance of males, the ratio of males to females being 1.8 to 1. In a previous analysis⁷ of 113 cases of coronary disease in nondiabetics that came to necropsy the proportion of males to females was 3 to 1. The greater susceptibility of the male to arterial disease, and especially coronary sclerosis, is well known. There is an indication that in diabetes the tendency to coronary arterial change is almost as great in the female as in the male. This is true not only of the coronary arteries but even more so for the peripheral vessels. Of 21 instances of peripheral gangrene there were 12 females and 9 males. This series is too small to draw definite conclusions, but it suggests that the comparative resistance of the female to the development of arterial disease is distinctly lessened when diabetes is present.

TABLE 2.—SEX DISTRIBUTION OF CORONARY DISEASE IN DIABETICS.

	Autopsies.	Coronary sclerosis.	
		No. of cases.	Per cent.
Males	57	29	50.9
Females	43	12	28.0

Table 3: The weight of the heart was recorded in 98 of the cases. Although no exact figure of heart weight can be given as the upper limit of normal, it is probable, according to Bell and Clawson,⁸ that the normal weight seldom exceeds 400 gm. in the female and 450 gm. in the male. When a heart weight above these limits is not associated with such conditions as valvular disease, adherent pericardium, syphilitic aortitis, chronic glomerulonephritis and hyperthyroidism, it may be assumed with few exceptions that primary hypertension was present in life. Using 450 gm. as the upper limit, 17 of the 98 cases, or 17.3 per cent, showed evidence of hypertrophy. In 2 instances there was an explanation in the heart for hypertrophy, in 1 case an old rheumatic mitral lesion, in the other a luetic aortitis. There were 86 autopsies above the age of 40 years and 15 cases of idiopathic hypertrophy occurred above

this age, giving an incidence of 17.8 per cent. Bell and Clawson,⁸ using otherwise unexplained cardiac hypertrophy at autopsy as evidence of hypertension, found that 13.3 per cent of males and 10.9 per cent of females over 40 years of age had primary hypertension. Using this criterion, there is indication that hypertension is but slightly more frequent in the diabetic than in the general population. Opinion has been divided regarding the blood pressure in diabetes. It has frequently been stated that diabetes is a cause of hypertension. The observations of Major⁹ indicate that hypertension is not a prominent feature even in the elderly diabetic. This is in agreement with the conclusions which may be drawn from a study of the heart weights in Table 3. It is noteworthy that of the 15 cases of hypertrophy 12, or 80 per cent, showed extensive coronary disease. Bell and Clawson emphasize the frequent association of coronary lesions and hypertensive heart disease. They found severe coronary disease in approximately 40 per cent of necropsies showing hypertensive heart above the age of 50 years. This indicates that coronary disease is twice as frequent in the hypertensive with diabetes as in the uncomplicated hypertensive heart.

TABLE 3.—WEIGHT OF HEART IN 98 AUTOPSIES ON DIABETICS.

Grams.	Heart weight.	
	Coronary.	Noncoronary.
100 to 199	0	1
200 to 299	3	25
300 to 399	8	21
400 to 499	20	8
500 to 599	9	2
600 to 699	1	0
<hr/>		
Below 450 grams	29	52
Above 450 grams	12	5

Coronary Disease and Peripheral Gangrene. Of the 100 autopsies, gangrene of the lower extremities of a mild or severe degree was present in 21 instances. There were 12 females and 9 males in this group. They were distributed according to age as follows: 1 between 40 and 50 years, 7 between 50 and 60 years, 10 between 6 and 70 years and 3 between 70 and 80 years. Of the 21 autopsies showing peripheral gangrene severe coronary disease with occlusion was present in 13, or 62 per cent. Wilder,⁴ from a study of 58 autopsies, found a high degree of coronary sclerosis in 75 per cent of diabetics with gangrene. It is important that the frequency of this association should be recognized. The probability of cardiac involvement should be taken into account, since surgical treatment is frequently considered in the diabetic with gangrene. This should add weight in the direction of conservative treatment and emphasize the study and care of the heart when more radical measures are necessary.

Aside from coronary disease there was little other cardiac change in the 100 autopsies. There were 3 cases of hypertrophy characteristic of hypertension heart with slight sclerosis but patent coronary vessels. All 3 died of congestive failure. There was 1 case of lues of the aortic orifice with aortic regurgitation. There was 1 instance of chronic rheumatic mitral valve defect. That there is a striking infrequency of rheumatic valvular disease in diabetes is emphasized by Joslin.¹⁰ He states that up to 1917 he could recall no case of diabetes under 50 years of age in which the patient complained of shortness of breath or presented the signs of an incompetent heart due to valvular disease of a definite and unquestionable rheumatic origin. Later several such cases did come under his observation. In a series of 56 autopsies upon diabetics at the Deaconess Hospital there was but 1 case of rheumatic heart disease. In reviewing the histories of diabetics, on the other hand, rheumatic fever is not uncommon. Barach¹¹ noted an incidence of 16 per cent in 226 cases. However, in 37 diabetics with a past history of rheumatic fever there occurred but 1 case of valvular heart disease. This indicates a definitely reduced incidence of cardiac involvement, since ordinarily it is estimated that rheumatic fever is followed in approximately 40 per cent of the cases by chronic valvular disease. Barach concludes that when a potential diabetic suffers an attack of rheumatic fever the heart is relatively immune to involvement. Joslin suggests the explanation that few children or young adults with severe rheumatic heart disease live through the 25 or 35 years that are necessary to bring them to the age when diabetes is common.

Another type of pathologic change which occurred in this series was a pale, swollen and cloudy heart muscle, the picture of a toxic myocardium. This was present in practically every case in which death was due to acidosis and coma. Foster,¹² in studying the pathologic changes in diabetes, noted myocardial degeneration at necropsy in every case of coma. This suggests the possibility that the circulatory insufficiency which occurs in diabetic coma may in part be due to this toxic myocardial change.

The exact mode of death could not be determined in every case of coronary disease, but in 35 the manner of death was quite definite. The causes of death in these 35 cases were as follows: A cardiac death occurred in 18, of which 11 were congestive heart failure and 7 anginal. The 17 noncardiac deaths were due to the following causes: gangrene, 7; cerebral accident, 4; coma, 1; pneumonia, 1; cellulitis, 1; mesenteric thrombosis, 1; accidental, 1; suicide, 1. In none of this latter group were there any clinical features indicative of heart disease. It is evident that coronary disease must be suspected in the diabetic even though a clinical picture of heart disease is absent.

Comment. There is no generally accepted explanation for the prevalence of arteriosclerosis in diabetics. Joslin¹ believes that the

arteriosclerosis is secondary to the diabetes and that the duration of the disease is an important factor. He has found that diabetes of 5 years' duration or longer is practically always accompanied by some degree of arterial change. Joslin strongly favors the theory that the cholesterol which is usually increased in the diabetic's blood is the basis for the vascular change. He is influenced in this by the work of Aschoff, who believes that an increased amount of cholesterol in the blood is one of the prerequisites for arteriosclerosis. The sclerotic change follows a fatty deposition on the arterial walls, especially at points subject to mechanical strain. As support for his views Aschoff points to the many feeding experiments in rabbits, in which prolonged administration of cholesterol has almost uniformly been followed by typical changes in the aorta. Although this theory seems to apply to the conditions which exist in diabetes, there is little or no evidence at the present time that such a process actually takes place.

A different explanation for the association of arteriosclerosis and diabetes is that the diabetes is a result of a generalized arteriosclerosis which also involves the pancreas. The elderly diabetic has frequently been termed the arteriosclerotic diabetic, implying that the arterial disease is the primary process. This theory suggests itself because of the fact that severe arterial disease in diabetes occurs almost entirely at an age period when arteriosclerotic changes are frequent. It cannot be denied that difficulties arise when we attempt to determine etiologic relationships for arteriosclerosis at a period of life when the normal individual is subject to vascular changes. However, there are several studies in young diabetes at age periods when sclerotic changes are ordinarily infrequent, which indicate a high incidence and early development of vascular change. Allbutt,¹³ discussing the relationship between diabetes and arteriosclerosis, states that "a plausible suggestion is that the glycosuria might be a result of arteriosclerosis in particular areas as, for example, the pancreas." He continues, however, with the statement that this conception occurred to him before he had an opportunity of witnessing the gradual advance of vascular changes as a sequel to diabetes in young persons. Allbutt noted many instances of thickened arteries in children and comparatively young adults, one of the youngest being a girl, aged 14 years.

Joslin,¹⁴ in a study of 52 autopsies, found an incidence of arteriosclerosis of 20 per cent in the second decade and of 59 per cent in the third decade. He mentions a boy whose diabetes began at 10.5 and ended 5.5 years later. The atheromatous plaques in his aorta were plainly evident and not at all to be confused with the minor alterations which occur normally at puberty. Joslin¹⁵ also cites the results of the roentgenologic studies made upon 324 of his diabetics by Morrison and Bogan. Roentgen ray evidence of arteriosclerosis was found in 30 per cent when diabetes began between the ages of

20 and 29 years and in 45 per cent when the onset was between 30 and 39 years. Using the same method in nondiabetics, Bowen⁵ noted an incidence of 0.5 per cent in these age periods. More recently Shepardson,¹⁶ also using the Roentgen ray, studied 50 diabetics who were under 40 years of age and in whom the disease had been present for at least 5 years. The average age of the entire group was 23.4 years and 36 per cent showed evidence of vascular sclerosis. This high incidence of arteriosclerosis in the young diabetic indicates that the vascular lesion is an accompaniment of the diabetes gradually increasing in degree with the progress of the disease. Although this does not necessarily mean that the diabetes is the cause of the arteriosclerosis, the evidence is strongly against the conception that the diabetes is secondary to the vascular disease.

Bowen studied the development of arteriosclerosis by means of the Roentgen ray over a period of 3 and 4 years in a group of diabetics who were properly treated and also a group in whom the disease was not well controlled. He describes a greater tendency toward increase in degree of arteriosclerosis in the poorly treated cases. Bowen concludes that the development of severe vascular disease requires several years of neglect of the diabetes. This may explain the relatively low incidence of severe vascular pathology in early life. In the young individual neglected diabetes is rarely of long duration, as there is usually an early fatal outcome. In the elderly the disease is typically mild and frequently symptomless, so that it may go on for a long period without proper treatment and thus lead to the development of extensive vascular disease. A high degree of vascular disease may be found in the young individual if he survives for a period of 10 years or more. This is illustrated in the following case, which has been reported in detail by Dr. Karl Anderson.¹⁷ A white male died at the age of 33 years of cardiac decompensation. Diabetes had been present for 14 years. At autopsy the heart weighed 440 gm. The descending branch of the left coronary artery showed marked sclerosis, the lumen being almost obliterated in places. The right coronary showed extensive thickening but was less involved and there was also a thrombus in this vessel. The pancreas appeared normal and the vessels did not show extensive sclerosis. The renal arteries were severely involved and the lumina markedly reduced. The abdominal aorta showed extensive intimal thickening with several ulcerated areas. Further evidence against the conception of the vascular pathology as the primary process is that in practically every instance in this series of autopsies the history of diabetes preceded the manifestations of the vascular disease by a variable period of time. Joslin,¹⁸ in discussing a group of 122 cases of angina pectoris associated with diabetes, states that the onset of the diabetes distinctly preceded that of the angina in 106.

At the present time it does not seem justifiable to conclude that diabetes is the causative factor in the arteriosclerosis, as no mechanism for this process has been satisfactorily proved. However, there appears to be sufficient evidence that the vascular disease either occurs coincidental with or as a sequel to the diabetes.

Conclusion. 1. An analysis of 100 autopsies upon diabetics shows an incidence of 41 per cent of severe coronary disease. Above the age of 50 years the incidence is 52.7 per cent as compared with 8 per cent in an even larger series of nondiabetics of the same age.

2. The frequency of coronary disease is almost as high in the female as the male.

3. The incidence of hypertensive hypertrophy of the heart indicates that hypertension is only slightly more frequent in the diabetic than the nondiabetic.

4. In diabetics with gangrene the incidence of coronary disease is higher than in the uncomplicated cases.

5. The essential cardiac lesion of diabetes is coronary sclerosis. Other types of cardiac disease are of relatively rare occurrence.

6. The etiologic relationship between diabetes and arteriosclerosis is discussed.

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DIABETIC GANGRENE: INCIDENCE AND PATHOGENESIS: AN ANALYSIS OF 58 CASES AMONG 1008 DIABETICS.*

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THE association of gangrene with diabetes was first mentioned by Marchal (de Calvi¹) in 1852. Since then numerous contributions have appeared in the literature. That gangrene may develop in diabetics is a well-known fact. Various types of gangrene may be found in this group of individuals. The arteriosclerotic form is quite common; obliterative endarteritis is less commonly found; embolic gangrene and thromboangiitis obliterans are relatively rare. There has been considerable discussion as to the status of what has been termed diabetic gangrene. Is there a form of gangrene with sufficient characteristics and clinical findings to warrant a diagnosis of diabetic gangrene thereby establishing its entity? Many authorities insist that one cannot definitely say upon examination of a section of the involved artery whether it is or is not due to a diabetic condition. In other words, their contention is that the arterial lesions are so closely related with the findings in arteriosclerotic gangrene that they can make no distinction between them, concluding therefrom that in diabetes what some term diabetic gangrene is really arteriosclerotic gangrene. Buerger,² Beard,³ and others have taken this attitude. Whether or not they are justified in discouraging the acceptance of diabetic gangrene as a separate form remains to be seen.

On the other hand, McKittrick and Root,⁴ Warren,⁵ and others have called attention to certain facts and clinical findings which are apt to exist in certain cases of gangrene in diabetics. These findings appear so regularly in this group of cases that even if the microscope does not establish a distinctive form, surely there may be enough evidence clinically to warrant a diagnosis of diabetic gangrene.

The following description of what may be termed diabetic gangrene is usually met with in this group of cases. Although occurring in the aged, it may make its appearance in the fifth decade. Its onset is usually insidious. An unrecognized cellulitis or osteomyelitis of the smaller bones in the foot is frequently responsible for the gangrene. Pain need not be a prominent symptom and sometimes its absence is a striking phenomenon despite the extensiveness of the lesion. Infection, suppuration and sloughing are commonly present. When ulcers develop from the gangrenous processes of the soft

* Read before the Southeast Branch of the Philadelphia County Medical Society.

parts, they may show marked undermining of the edges and an extensive sloughing of the tissues that could not be appreciated by external examination alone. The arteries may not show the pathologic changes that one meets in arteriosclerotic gangrene. This holds true for some cases where despite extensive involvement of a gangrenous process, the dorsalis pedis artery may have a normal pulse and the roentgenographic examination may fail to reveal calcific deposits in the walls of the vessels. Thrombophlebitis is frequently found. The gangrene does not seem to conform to the dry form expected in arteriosclerotic type, rather, it is of the moist variety. It may extend laterally and involve contiguous structures, whereas in arteriosclerotic gangrene there usually is mummification of a toe and if there is extension it is apt to be limited to an area supplied by the same vessel.

For the sake of convenience the clinical facts which may aid in distinguishing between the two types of gangrene are presented in tabular form:

TABLE 1.—SHOWING POINTS OF DIFFERENTIAL DIAGNOSIS BETWEEN DIABETIC AND SCLEROTIC GANGRENE.

	Arteriosclerotic.	Diabetic.
Age	Senile, usually in 7th decade	May occur in 5th or 6th decade.
Pain	Usually severe even with small area of gangrene	Varies; may be absent or mild in early stages.
Infection	Not present	Nearly always present; may have considerable sloughing.
Type of gangrene	Dry	May be dry, but more commonly moist.
Line of demarcation	Present	Often absent.
Extension	Along lines of arterial supply	May extend laterally as well.
Pulse	Absent or markedly diminished	May be present in some cases.
Roentgen ray	Calcification of walls of arteries	Arteries may show no demonstrable pathology.
Pathologic findings	Thickening of the walls with calcific deposits	Atheromatous changes with thrombosis; calcification may or may not be present.
Microscopic appearance of vessels	Medial form of sclerosis	Intimal form of sclerosis.

Incidence of Gangrene in Diabetes. Any attempt to arrange statistical data concerning the frequency of gangrene in diabetes meets with difficulties. The following points arise: First, the period over which the records were accumulated is important. One invariably finds a higher percentage of cases of gangrene in the recent years than preceding periods for obvious reasons. In the later periods, insulin has preserved more patients from the earlier complications, the disease is generally being more efficiently handled and we are now more acutely aware of gangrene than ever before.

Second, the source of the records, whether from office practice, outpatient departments or from hospitals is to be considered. The data collected from patients in institutions will show a higher rate of incidence because as a rule those patients with complications and the severer forms of diabetes are more likely to seek hospital aid. A fairly large number of milder forms of diabetes will not or cannot go to the hospital. This will keep the number of cases of diabetes in hospitals at a lower level and will apparently result in a higher percentage of gangrene. This need not necessarily apply to all hospitals. I have in mind as an exception the New England Deaconess Hospital where Joslin's statistics have been gathered.

The third difficulty is the question as to what constitutes a case of gangrene. One may see a patient with circulatory disturbances with discoloration of a toe or two, but the process does not eventually materialize into gangrene. On the other hand, a diabetic may have circulatory disturbances with marked symptoms and only one or two small spots of gangrene. There may be still a third group with definite evidences of deficient circulation but no apparent signs of destruction of the tissues.

With these facts in mind, the author suggests that all cases showing circulatory disturbances of the extremities be classified in three groups:

GROUP 1. *Gangrene.* Diabetics who have unmistakable signs of gangrene. As a rule, the lower extremities are involved, either the toes, heel or soft parts of the legs. Other areas such as the lungs, buttocks, nose and genitalia may be involved, but they are comparatively rare and have not been included in the author's statistics. This group embraces the various forms of gangrene: the arteriosclerotic, embolic, thromboangiitis obliterans and the so-called diabetic gangrene.

GROUP 2. *Impending or Threatened Gangrene.* Where patients present not only signs of impaired circulation but also definite evidences of trophic disturbances, which have progressed to such a degree that they almost develop gangrene. The typical case is one in which there is a deep seated infection in the foot with swelling and there is encroachment upon the blood supply to the toes by pressure. Usually one finds a purplish discoloration of one or more toes, with coldness of the distal parts. There may be an ominous discoloration of the adjacent tissues. However, in time these signs subside and gangrene is averted. In this class may be included the trophic ulcers which in time may lead to gangrene.

GROUP 3. *Potential Gangrene.* The third group is suggested for those diabetics who have symptoms or signs of deficient circulation. Evidences of an altered circulation may be recognized by the presence of lesions: red spots, scars, scarlike depressions and blebs or by the various methods of studying the circulation, particularly the oscillometer, reaction of the skin to histamin inoculations and

Roentgen ray. The above lesions⁶ and descriptions of these methods⁷ of investigating the circulation have been described in previous publications.

Analysis of Records. Analysis of 1008 cases of diabetes was made in an effort to see what can be learned in reference to circulatory disturbances as a complication in this disease. These records cover a period of 11 years: 1920 to 1930. The patients were studied chiefly in office practice and the outpatient department. A small number were observed in institutions.

TABLE 2.—SHOWING STATISTICS OF 1008 CASES OF DIABETES MELLITUS WITH REFERENCE TO INCIDENCE OF GANGRENE AND CIRCULATORY DISTURBANCES.

Period.	Total No. cases.	Number of cases of gangrene.		Percentage.
1920-1930	1008	Group I: Gangrene . . .	58	5.75
		Group II: Threatened . . .	28	2.77
		Group III: Potential . . .	89	8.82
		Total cases with circulatory disturbances	175	17.3
(a) 1920-1925	345	Group I: Gangrene . . .	13	3.8
		Group II: Threatened . . .	7	2.03
		Group III: Potential . . .	24	6.95
		Total cases with circulatory disturbances	44	12.75
(b) 1926-1930	663	Group I: Gangrene . . .	45	6.78
		Group II: Threatened . . .	21	3.16
		Group III: Potential . . .	65	9.80
		Total cases with circulatory disturbances	131	19.75

A glance at the above table shows that 58 cases of gangrene were observed in the entire series of 1008 cases of diabetes, giving a percentage of 5.75. If the threatened cases are included with those of actual gangrene, the percentage would be increased to 8.53 and if all the 3 groups are taken collectively, the incidence of circulatory disturbances in diabetics would rise to 17.3 per cent, or practically 1 patient out of every 6 has evidences of circulatory disturbances and 1 out of every 17 to 18 diabetics has developed gangrene. This is based on the group from 1920 to 1930. The incidence of the various groups of complications is somewhat higher if we confine ourselves to the recent 5-year-period from 1926 to 1930. It is plausible to assume that this percentage indicates more accurately the tendency for the development of complications. During this 5-year-period, 663 cases were observed; 45 patients developed gangrene (6.78 per cent); there were 21 cases of impending gangrene (3.16 per cent) and 65 cases of what we may term potential gangrene (9.80 per cent). Collectively, there were 131 patients out of 663 who showed evidences of impaired circulation, with and without gangrene. In other words, 1 out of every 5 patients showed some evidence of arterial disease.

It may be of interest to compare the author's figures with those reported by others. This has been arranged in Table 3.

TABLE 3.—SHOWING THE COMPARATIVE STATISTICS OF GANGRENE AS A COMPLICATION IN DIABETES.

Reported by.	Hospital.	Period.	Total diabetics.	Gan- grene.	Per- centage.
Blotner and Fitz	Peter Bent Brigham Hospital, Boston	1913-1925	969	69	7.0
McKittrick and Root	New England Deacon- ess Hospital	1923-1928	4066	163	4.08
Wendt and Peck	Grace Hospital and office, Detroit	1919-1929	1073	113	10.7
Futcher	Johns Hopkins Hospital	1889-1925	1025	49	4.5
Coller and Marsh	University Hospital, Michigan	1921-1925	650	20	3.2
Lemann	New Orleans Hospital and office	1921-1926	471	25	5.3
Paullin (quoted by Lemann)	Georgia Charity Hospital, New Orleans	1921-1926 1921-1926	560 439	15 79	2.65 18.0
Lemann ^s	Touro Infirmary, New Orleans	1921-1926	201	20	10.0
	Boston City Hospital	1921-1926	967	109	11.2
	Mass. General Hospital	1921-1926	600	58	9.0
	Montreal General Hos- pital	1921-1926	1016	36	3.5
Mean average		Total diabetics:	12037	756	6.28
Author's	Office and Outpatient	1920-1930	1008	58	5.75

Pathologic Anatomy of Diabetic Gangrene. The appearance of the extremity varies according to the type of gangrene. In the embolic form, the leg is swollen, moist, extensive involvement, with large bleb formation and a foul odor. The gangrene of thromboangiitis obliterans is a slowly developing one with trophic disturbances, intense pain, often associated with recurring thrombophlebitis, occurs earlier in life than the other forms. The veins as well as the arteries are involved. There is extensive occlusion of the vessels, with distinct evidences of inflammation. Adhesions between the vessels and the accompanying nerves are often found. The thrombus in the lumen may show organization and canalization. Sporadic cases occur in diabetes but they are relatively rare and it is questionable whether the diabetes has any influence upon the production of the gangrene. Judging from the rarity of this combination, when it does occur, the probabilities are that the diabetes developed after the thromboangiitis.

ARTERIOSCLEROTIC GANGRENE is easily recognized by the dry mummification of the tissues. There is a sharp line of demarcation. There may be considerable pain especially when there is ulcer formation. Evidences of arteriosclerosis are present. It usually occurs in the seventh decade or in older individuals. The extension of the gangrene is slow. Infection may or may not exist. If infection is superimposed upon the dry gangrene, extension of the gangrenous process may take place rapidly.

DIABETIC GANGRENE, as mentioned above, has certain characteristics which may be briefly summarized, even at the risk of repetition. Its frequent association with or relation to infection; its occurrence in the fifth or sixth as well as the later decades; the tendency to involve soft parts; the moist type of gangrene; absence

of a line of demarcation; absence of evidences of arteriosclerosis such as the persistence of the dorsalis pulse and negative Roentgen ray findings; the tendency to extensive sloughing and the likelihood of recovery without amputation. The arteries macroscopically may be rigid and the lumen may be occluded. The walls of the vessels are thickened. The occlusion of the lumen may be due to proliferation of cells from the intima, atheromatous plaques and calcific material or it may be the result of a secondary thrombosis. Microscopically, Warren⁹ emphasizes atheromatous changes of the vessels, particularly of the intimal type. This type can be recognized by "local thickening and hyalin change of the intima with lipoid infiltration, the presence of cholesterol crystals or the presence of calcified deposits. These changes are practically always accompanied by fraying or reduplication of the internal elastic lamina."

The above may and may not be associated with calcific changes of the vessels because gangrene usually appears in diabetes in the decades when arteriosclerosis is likely to develop.

Another observation by Warren¹⁰ is of interest. He noticed that many of the arteries showed "an infiltration, frequently intimal, with polymorphonuclear or more rarely mononuclear leukocytes."

The veins as a rule exhibit no striking pathologic changes. There may be some thickening of the larger veins and some cellular infiltration but nothing that can be attributed to diabetes. They receive only the slightest comment in the various contributions on diabetic gangrene. In his studies on impending gangrene, Bernheim¹¹ emphasizes the prominence and bulging out of the veins when standing. Others have mentioned thrombophlebitis. Collier and Marsh¹² mention varicose veins in those diabetics with intractable leg ulcers, but were rarely involved in the group with gangrene. In our series of observations, thrombophlebitis was by no means uncommon. However, the presence of thrombophlebitis may be merely incidental and has no influence upon the development of the complications.

Mechanism of Diabetic Gangrene. There are three forces which are at work producing this condition: (1) Diabetes; (2) changes in the arterial system, and (3) infection. Much has been written about the rôle of diabetes in the production of atheromatosis and arteriosclerosis. The hyperglycemia, the increase in lipoids, the hypercholesterolemia, the acidosis, all seem to have some influence, particularly upon the intima, resulting in various pathologic changes. These in turn may develop into a full blown picture of atherosclerosis. Add to this the usual tendency for the appearance of calcific changes in the vessels and we have briefly a picture of what takes place in the arteries of a diabetic past middle life. The consensus of opinion suggests that a period of 5 years of the diabetic condition is usually found in these cases. However, there are exceptions to this rule.

In time there is a gradual encroachment upon the lumen of the vessels. This may be due to a thickening of the walls or may be the result of thrombus formation. However, regardless of the underlying cause, the result is the same and that is a definite impairment of the blood supply to the parts. This deficiency of circulation results in trophic disturbances and lowers the resistance of the tissue to infection. The disturbance of blood supply will depend upon the rapidity with which these pathologic changes take place. If their development is slow, requiring a period of months before occlusion takes place, nature makes up for this deficiency by the establishment of a collateral circulation. In some cases the extent of this collateral blood supply is very striking. In his contribution on the collateral circulation of the extremities, Bernheim¹³ has noticed that extensive occlusion of the main branches may be compensated for by the development of a collateral circulation from small insignificant branches.

The patient may be fortunate in having established a collateral circulation which may practically compensate for the lack of blood supply. Complications may be warded off indefinitely, provided this even balance is maintained. These individuals are always potential cases of gangrene. Any added strain upon the circulation, progression of the disease, or infection however slight may alter the balance and gangrene sets in. Sometimes this complication makes its appearance despite all precautions and care.

Infection is an important factor in the development of gangrene. It is almost invariably present in the so-called diabetic gangrene and may be responsible for its development. Sometimes the infection gains entrance through insignificant crevices of a callus or a break in the skin from minor cuts or abrasions such as the trimming of a corn, cutting toe nails or irritation of the skin from ill-fitting shoes. The lowered resistance of the tissues and the deficient blood supply practically invite an infection and when entrance is once gained, extension of the process is a simple matter. In some patients the infection seems to develop from within. Attention has been called to the fact that an osteomyelitis of the metatarsals may exist without any external signs. It can only be detected by careful examination of the feet. The above facts are emphasized because they may be forerunners of a developing gangrene of the involved area and may shut off the blood supply to the toes by the pressure of the induration upon the already weakened arteries. This evidently is the clinical picture seen in those patients with impending gangrene who have deep-seated infections of the feet with discolored toes bordering on gangrene. The outcome depends upon the management of the case. With skillful handling, the infection may be controlled, and gangrene may be avoided in some cases.

Analysis of the Group With Gangrene. The statistics of the diabetics who developed gangrene are arranged in Table 4. From this

table one can learn some information as to the age, duration of the diabetes, and the end results, when obtainable.

AGE. All but 2 developed gangrene when they were past 50 years. The largest numbers occurred in the sixth and seventh decades. This finding is rather general when compared with statistics of others. Joslin¹⁴ reported that the average age at which gangrene developed in his series was 62 years; the youngest at 36 and the oldest at 82 years. The studies of Blotner and Fitz,¹⁵ and Eliason and Wright¹⁶ were similar to the above. While there may be some variation in the percentages of the sixth and seventh decades, the final analysis shows that the vast majority of cases complicated with gangrene occurs in those past 50 years.

SEX. In the author's series of gangrene, there were 37 females and 21 males. These figures differ from those of others. Blotner and Fitz in their series noticed that there were 38 males and 31 females. Similarly, Eliason and Wright mentioned 33 males and 32 females in their group. It is very doubtful whether any influence of sex can be attached to the development of gangrene.

TABLE 4.—SHOWING AGE, SEX, DURATION OF DIABETES AND RESULT OF THE 58 CASES OF GANGRENE.

Age. Decades.	Sex.			Years of duration of diabetes.					Result.	
	No.	M.	F.	1-2	3-4	5-9	10-14	15-20	Died.	Amputation.
40 to 49 .	2	2	0	0	0	2	0	0	2	2
50 to 59 .	20	7	13	3	4	6	3	4	3	6
60 to 69 .	32	12	20	7	6	6	7	6	10	4
70 to 79 .	3	0	3	0	1	1	1	0	0	1
80 . .	1	0	1	0	0	0	0	1	0	1
Total .	58	21	37	10	11	15	11	11	15	14

Duration of Diabetes. A 5-year-period of diabetes is usually noticed in those diabetics who show evidences of arterial changes. This observation has been confirmed by many. One must remember that this applies to changes in the vessels and is particularly applicable to the young.

Lest a false impression be made, it is worth mentioning the fact that gangrene may develop at any time in an aged diabetic. Arteriosclerosis may have already developed before diabetes comes on the scene. The surmise that this individual has an immunity against complications for 5 years is decidedly erroneous. There is no reason whatever why this diabetic may not develop gangrene at any time. Joslin,¹⁷ in his group of gangrene cases, noticed that 38 occurred in those who had diabetes between 1 and 4 years. In the author's series, there were 10 cases with a history of diabetes between 1 and

2 years' duration; 11 cases between 3 and 4 years; 15 cases between 5 and 9 years and 22 cases of gangrene occurred in individuals who had diabetes for 10 to 20 years. Twenty-one cases of gangrene developed in those who had diabetes less than the allotted 5-year-period, a percentage of 36.2. Of this group, 13 of the cases were in the seventh decade.

Results of Gangrene in Diabetics. Gangrene is now recognized as an important factor in the contributory cases of death in diabetes. McKittrick and Root¹⁸ mention gangrene as a contributory cause in 24.2 per cent of the diabetic deaths. Morrison's¹⁹ figures were 23 per cent; Rabinowitch²⁰ reported 39.1 per cent; Dublin,²¹ in a statistical analysis of 3386 deaths from diabetes in 1929 to 1930, mentions the influence of gangrene in 23 per cent of the deaths. In our series of 58 cases of gangrene, 15 died either following operation or where no surgery was attempted, a percentage of 26.

AMPUTATION. In Wendt and Peck's²² series of gangrene, 25 per cent resulted in amputation. In Joslin's clinic, McKittrick and Root²³ reported 157 operations upon 138 diabetics for lesions of the lower extremities, from January, 1923, to December, 1928. In this group there were 80 amputations for gangrene, 72 major and 8 minor operations.

The author's studies showed that 16 cases out of 58 resulted in amputation of the leg (27 per cent).

PROGNOSIS. The prognosis of the diabetic with gangrene may be considered from two standpoints, the immediate and the remote. The immediate prognosis depends upon the type and degree of the gangrene, plus the added risks of surgical procedure, if this form of treatment is decided upon. Some cases of gangrene develop quickly. Others have a less conspicuous beginning and for a long time may have no serious effects upon the general condition of the patient. This applies particularly to focal gangrene and the arteriosclerotic types with involvement of a single toe. Regardless of the benignity of a focal area of gangrene, every case should be looked upon as a serious one. They are always uncertain quantities until healing definitely takes place. They are always susceptible to added infection and when infection sets in, the problem is a grave one. Toxemia is the next development and is an important factor upon the ultimate outcome of the case.

Conservative treatment is advisable in the early stages of gangrene. Absolute control of the diabetic condition and local care of the involved part with measures directed toward the improvement of the circulation may control the gangrene. In some cases, particularly the so-called diabetic gangrene with involvement of the soft parts, the result may be extremely favorable. An occasional case may be cured. This form of treatment requires unlimited patience on the part of the physician; the recovery is a gradual and

long drawn-out process, often taxing the patience of the physician. However, when infection appears and begins to spread upward and general symptoms in the form of toxemia are manifested, it is time to act. A short period of observation may be in order to see whether or not the infection is merely a threat and can be controlled. If the toxemia persists and shows a tendency to progress, radical measures seem to be the only course to pursue. It is inadvisable to prolong the period of observation after the infection has spread beyond the foot and involves the leg, with general symptoms such as fever, sweats, weakness and rapid pulse. There is danger of damaging the myocardium to such a degree as to put it beyond repair after amputation has been performed.

The group of gangrene with amputation presents an unusual status when considering prognosis. In the past few years, thanks to insulin and proper medical care, hazards of surgery upon the diabetic have been eliminated. This pertains to major surgery as well as minor procedures. However, this does not apply to the group of amputations in diabetics. The mortality rate in this series is comparatively high. In the series of 69 cases of gangrene reported by Blotner and Fitz, 16 died while in the hospital. Of the 53 patients who were discharged, 42 were followed up and 5 died within 1½ years after they left the hospital, making a total of 21 deaths (30.5 per cent). In McKittrick and Root's studies, there were 14 deaths in the group of 80 gangrenes, giving an average of 17.5 per cent. However, this applies to the period of their stay in the hospital. In the author's series of 58 cases of gangrene, there were 15 deaths, giving a percentage of 26.

The causes of death in most of the above mentioned group of cases were septicemia and bronchopneumonia. Other causes worth mentioning are coronary artery disease and embolism.

The remote prognosis of the diabetic with amputation is by no means favorable. The forces which were responsible for the development of gangrene are still present. True, he may have learned his lesson and will be more careful in the future. Unfortunately the damage to the vessels cannot be undone. The liability of a recurrence is forever present and the necessity for double amputation is by no means rare.

The duration of life after operation in these diabetics is not so easily determined. Joslin in a recent address mentioned a period of 2 years as the average span of life after amputation for gangrene. No doubt, one will meet with patients who have lived longer than this term of years. One patient in the author's series lived for 5 years, another 3 years. However, when one realizes that nearly every diabetic with gangrene fundamentally has arterial disease and that these pathologic changes are general, involving the coronary arteries as well, with toxic phenomena affecting the various vital

structures added to the usual effects of the diabetic condition, is it any wonder that the outlook is a cheerless one?

Summary and Conclusions. Various types of gangrene may occur among diabetics. The arteriosclerotic type and the so-called diabetic gangrene are the most common. Thromboangiitis obliterans and embolic gangrene are less commonly seen.

The advisability of recognizing diabetic gangrene as a definite form is discussed. The fact that a certain number of cases with gangrene present clinical features and pathologic changes in the vessels, plus the fact that it may be of the moist variety, lend support in deciding that we are dealing with a form other than the well accepted arteriosclerotic type of gangrene.

In order to obtain more definite information concerning the frequency of gangrene and the influence of diabetes upon the vessels the various degrees of circulatory deficiency should be evaluated. They may be graded as potential cases of gangrene, impending and actual gangrene, according to the extent of the occlusion.

Analysis of 1008 cases of diabetes mellitus, observed during a period between 1920 and 1930, shows that there were 58 cases of existing gangrene (5.75 per cent); 28 cases of threatened or impending gangrene and 89 cases of potential gangrene. Collectively, the three groups totaled 175 cases (17.3 per cent) of circulatory disturbances found. In other words, 1 out of every 17 to 18 diabetics developed gangrene and 1 out of every 6 showed evidences of impaired circulation. If the more recent 5-year-period (1926 to 1930) is considered, the incidence is higher: 6.78 per cent developed gangrene and 19.75 per cent had deficient circulation in the extremities.

The author's figures compare closely with the average statistics of others. Out of 12,037 patients with diabetes, there were 756 cases of gangrene (a percentage of 6.28).

Diabetic gangrene is the end product of three main influences: the metabolic disturbances and their effect upon the vessels and the tissues, changes in the arteries with the resulting deficient blood supply to the parts, and infection.

Of the group of patients with gangrene, all but 2 developed this complication when past 50. Gangrene may develop at any time in the aged diabetic. There were 10 cases of gangrene among those who had diabetes between 1 and 2 years, and 11 cases between 3 and 4 years.

Of the 58 cases of gangrene, 16 resulted in amputations (27 per cent).

The prognosis for the diabetic with gangrene is uncertain. There were 15 deaths in the author's series (26 per cent). This included both the surgical cases and those patients who declined operations. The future of the diabetic who has once had gangrene is fraught

with danger. He is always liable to a recurrence of the complication. The average span of life for those who have had gangrene with amputation of the extremity is considered to be about 2 years.

To lower the incidence of gangrene in the diabetic and to increase his span of life, one must have cognizance of the high incidence of circulatory disturbances in these patients. Early recognition of arterial changes and an intelligent attempt to correct and improve the circulation may ward off complications until a sufficient collateral circulation has been established to make up for the deficient blood supply to the parts.

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THE EFFECT OF LUGOL'S SOLUTION ON CHRONIC LYMPHATIC LEUKEMIA AND ITS BEARING UPON THE PATHOGENESIS OF EXOPHTHALMIC GOITER.

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The Basal Metabolism in Disease. Other than exophthalmic goiter, the basal metabolic rate is significantly elevated in various clinical conditions, such as the leukemias, polycythemia vera and the nonleukemic lymphoblastomata (Kraus,¹ Boothby and Sandiford,² Riddle and Sturgis,³ Krantz and Riddle,⁴ Abbott,⁵ Isaacs,⁶ Krantz⁷). Although there is considerable variability in the literature, the consensus of opinion is that there may be a significant increase in oxygen consumption in certain patients with pernicious anemia, essential hypertension, acromegaly and diabetes mellitus (Meyer and DuBois,⁸ Boothby and Sandiford,² Strauss,⁹ Riesman,¹⁰ Mannaberg,¹¹ Boas and Shapiro,¹² Cushing and Davidoff,¹³ Joslin and Lahey¹⁴).

The increased basal metabolic rate in exophthalmic goiter has been variously attributed either to an excess (Möbius¹⁵) or an abnormality (Mayo and Plummer,¹⁶ Williamson and Pearse¹⁷) of thyroid secretion. Other glands of internal secretion, such as the adrenals and gonads have been considered by some as responsible for the clinical syndrome, and various portions of the central and sympathetic nervous systems have received similar attention.

There is just as little agreement, and possibly a group of more intangible hypotheses, concerning the nature and mechanism of the elevated oxygen consumption in the leukemias.

Although early investigators (Graefe¹⁸) suggested the relative importance of immature leukocytes in the maintenance of an increased basal metabolic rate in leukemia, subsequent clinical experience (Murphy, Means and Aub,¹⁹ Krantz,⁷ Riddle and Sturgis,³ Krantz and Riddle,⁴ McAlpin and Sanger,²⁰ Gunderson²¹) has demonstrated that there does not seem to be an *invariable* relationship between the total white blood cell count, state of maturity of leukocytes and the height of the basal metabolic rate. Although these factors sometimes vary simultaneously in the same direction, the association is certainly not a *constant* one.

The suggestions concerning the mechanism of the elevated basal metabolic rate in acromegaly, diabetes mellitus, essential hypertension, pernicious anemia and the nonleukemic lymphoblastomata seem to be based mostly upon speculation. However, Isaacs⁶ has demonstrated in polycythemia vera that there is a definite relationship between the height of the basal metabolic rate and the uric acid production due to the destruction of nuclear material.

Finally, it seems of importance to note that the basal metabolic rate is not invariably elevated above normal even in exophthalmic goiter and the chronic leukemias; and it is also of interest that Kessel and Hyman,²² Friedgood²³ and others have reported a clinical syndrome (autonomic imbalance, sympathotonia, formes frustes hyperthyroidism) indistinguishable from exophthalmic goiter with the exception of a normal basal metabolic rate.

It is obvious, therefore, that although considerable investigation has been directed toward the discovery of the cause or causes responsible for the increased oxygen consumption in these diverse maladies, the entire problem has successfully resisted a satisfactory solution.

Nature of the Present Investigation. The remarkable effect of Lugol's solution on the elevated basal metabolic rate, pulse rate and clinical symptoms of exophthalmic goiter naturally suggested investigation of its activity on similarly increased oxygen consumption in conditions other than Graves' syndrome. The present series of observations, therefore, were made in the belief that under properly controlled conditions, valuable information could be ascertained concerning the mechanism involved in the production and maintenance of the elevated basal metabolic rate not only in Graves' syndrome, but also in the other diseases characterized by this phenomenon. It was also hoped that further investigation would result in a clearer conception of the pathogenesis of exophthalmic goiter and the nature and significance of the iodine reaction.

Lugol's Solution in Graves' Syndrome. The effect of iodine in exophthalmic goiter is well defined and widely recognized. It is of interest, however, to emphasize several of the more significant characteristics of the iodine reaction.

Lugol's solution will depress the elevated basal metabolic rate and tachycardia, and ameliorate the peculiar nervous manifestations of the disease in favorable cases of exophthalmic goiter.

However, iodine does not always induce such a remission, nor does it materially influence the progress of the disease itself, except that it may temporarily alter the character and intensity of the symptoms (Means and Richardson,²⁴ Barker²⁵).

Finally, there is evidence to believe that the characteristic response to iodine is dependent upon the geographic area in which the case originates (Coller and Potter²⁶); and that the higher the basal metabolic rate before administration of iodine, the greater is the expected percentage drop in the rate following treatment. It is also true, conversely, that the decrease from the original basal rate is relatively small, if the initial rate was only moderately increased (Means and Richardson,²⁴ Coller and Potter²⁶).

Effect of Iodine in Experimental Hyperthyroidism and on Normal Human and Animal Controls. These clinical observations assume even greater significance when it is emphasized that iodine has no effect whatsoever in altering the clinical symptoms, increased

basal metabolism and pulse rate induced by the ingestion of thyroid extract in man, and that it does not accelerate recovery from the true state of hyperthyroidism thus produced (Carson and Dock,²⁷ Sturgis,²⁸ Means and Richardson,²⁴ Starr, Walcott, Segall and Means²⁹). Martin,³⁰ Read, Walker and McKenney,³¹ Snell, Ford and Rowntree,³² and Liebesney³³ conclude that iodine has no appreciable effect in normal human beings, and Liebesney³³ suggests that it may even be associated with a tendency to increase the basal metabolic rate.

Sturgis, Zubiran, Wells and Badger³⁴ and Kunde³⁵ have definitely demonstrated that iodine is ineffective in influencing or preventing experimental hyperthyroidism in animals, contrary to the experiments of Hildebrandt³⁶ and Blalock and Harrison.³⁷

Lugol's Solution in Morbid Conditions Other Than Exophthalmic Goiter. Martin³⁰ has recorded his investigations concerning 2 cases each of "small cell" lymphatic leukemia and polycythemia vera which he treated with 5 drops of Lugol's solution 3 times a day. These patients failed to show any change in basal metabolism. However, 4 patients with pernicious anemia and 2 cases of afebrile convalescent rheumatic fever showed a definite depression in their basal metabolic rates by the 14th day of treatment.

Cushing and Davidoff¹³ have reported a single case of acromegaly (hyperpituitarism) which they considered free of "hyperthyroidism," and in which the basal metabolism and pulse rate rapidly decreased following treatment with Lugol's solution just as occurs in exophthalmic goiter; however, they concluded that the elevation of the metabolic rate (+40 per cent) "might be properly ascribed to the hyperpituitarism."

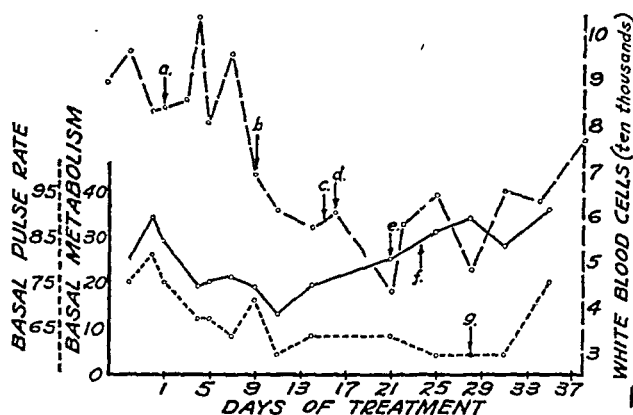
Additional experience in this clinic³⁸ (data unpublished as yet) shows that iodine had a definite effect in decreasing the basal metabolic and pulse rates in one case each of polycythemia vera and acromegaly. Its effect in chronic myelogenous leukemia is questionable.

Clinical Methods and Procedure. Ten patients with chronic lymphatic leukemia were treated with Lugol's solution (usually 1 cc. 2 or 3 times daily) over a period of several weeks, when the clinical condition of the patient allowed this interval of study. This procedure was not adopted in those patients suffering from severe anemia and in immediate need of transfusions.

Determinations of the basal metabolic rate, basal pulse rate, basal weight and blood studies were carried out during this period of study. The basal metabolisms were determined in the routine manner with the closed-circuit Roth-Benedict apparatus.

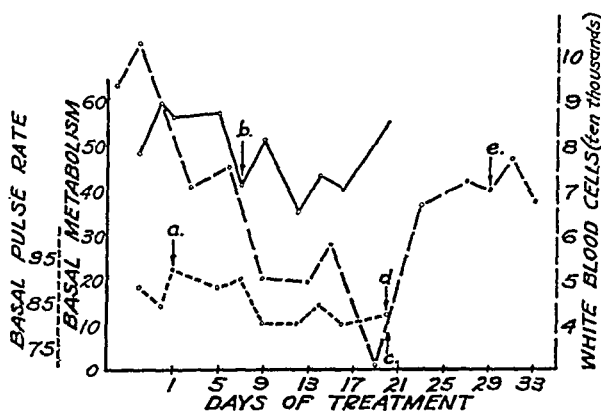
All of the patients who eventually showed a significant response to Lugol's solution were ambulatory, and in most cases attending the medical out-patient department. Nevertheless, the control period, even in these cases, extended over several days to 2 weeks.

These precautions were necessarily taken because of the widely recognized fall in basal oxygen consumption following general hospitalization and subsequent mental as well as physical relaxa-



Basal metabolism ——— Basal pulse rate - - - - -
White blood cells ——— . ———

CHART I.—*Patient No. 1.* Changes in basal metabolism, pulse rate and leukocytes during treatment. *a*, Started Lugol's solution, gtts. xv b.i.d.; *b*, Lugol's solution increased to gtts. xv t.i.d.; *c*, Lugol's solution temporarily discontinued; *d*, Vincent's angina with temperature of 102° F. Possibly an exacerbation of leukemic process; *e*, Roentgen ray treatment over inguinal lymph nodes. White blood cell count taken before treatment; *f*, Lugol's solution resumed, gtts. xv b.i.d.; *g*, persistent bradycardia associated with increased basal metabolic rate.



Basal metabolism ——— Basal pulse rate - - - - -
White blood cells ——— . ———

CHART II.—*Patient No. 2.* *a*, started Lugol's solution, gtts. xv b.i.d.; *b*, basal metabolism determined 35 minutes after 0.060 gm. codein phosphate (*h*); *c*, transfused with 500 cc. citrated blood; *d*, persistent slow pulse associated with an increasing basal metabolic rate; *e*, Lugol's solution discontinued.

tion during the test period. Any changes, therefore, that occurred in basal metabolism, pulse rate or white blood cell count could not properly be attributed to prolonged hospitalization or bed rest.

Following the control period, the basal metabolism was determined every other day, starting on the third to the fifth day of treatment, and if a depression occurred, was followed, if possible, until it had definitely ceased to exhibit changes of any significance. The white blood cell counts were studied simultaneously.

Several of the patients had received Roentgen ray therapy from 1 to several months prior to treatment with Lugol's solution, and this fact is noted in conjunction with each case report.

Clinical Data. The charts and clinical notes which follow are concerned with the case histories and physical findings of 10 patients suffering from chronic lymphatic leukemia. The salient points in their clinical course prior to and after treatment with Lugol's solution are indicated schematically in Tables 1 to 5. The complete clinical data are presented graphically in Charts I and II, and are necessarily limited to a consideration of only 2 patients in order to omit superfluous detail and repetition.

TABLE 1.—SUMMARY OF CLINICAL HISTORIES IN 10 PATIENTS WITH CHRONIC LYMPHATIC LEUKEMIA.

Clinical symptoms.	Number of patients.
Asthenia	10
Ease of fatigue	8
Unusual nervousness	8
Abnormal irritability	8
Good appetite	5
Night sweats	5
Cough with expectoration	5
Dyspnea on exertion	5
Marked loss of weight	4
Bleeding gums	4
Precordial palpitation	4
Slight loss of weight	3
Abnormal increase of perspiration	3
Subjective increase of warmth	2
Abnormal increase of appetite	2
Diarrhea	2
Epistaxis	2
No loss of weight	2
Pleurisy	2
Moderate loss of weight	1
Appearance of diffuse skin pigmentation	1
Anorexia	1

Clinical Results. *Nature of the Symptomatic Remission.* The laws which apparently govern the response of exophthalmic goiter to iodine seem to apply, with remarkable similarity, to chronic lymphatic leukemia. However, the percentage frequency of this response in leukemia is smaller than that noted in Graves' syndrome.

Investigation of this series of 10 consecutive patients with chronic lymphatic leukemia revealed the fact that each one experienced a symptomatic remission within 24 hours to 10 days after the initial treatment with iodine was instituted. In 2 of these instances, it was only of relatively brief duration (about 2 weeks).

TABLE 2.—SUMMARY OF PHYSICAL SIGNS IN THE 10 PATIENTS.

Physical signs.	Number of patients.
General glandular enlargement	10
Splenomegaly	10
Pallor of skin and mucous membranes	6
Definite malnutrition	4
Bilateral exophthalmos with relatively greater prominence of the right eye	3
Dalrymple's eye sign positive	3
Bleeding gums	3
Unilateral prominence (exophthalmos) of right eye	2
von Graefe's eye sign positive	2
Kocher's eye sign positive	2
Leukemic retinitis	2
Conjunctiva visible below cornea with axis of vision in horizontal direction	2
Enlargement of submaxillary glands	2
Bilateral exophthalmos	1
Hepatomegaly	1
Diffuse brownish skin pigmentation	1
Purpura over lower extremities	1
Chronic myocardial insufficiency with normal blood pressure	1

TABLE 3.—DATA IN THE 10 PATIENTS BEFORE TREATMENT WITH LUGOL'S SOLUTION.

Number.	Sex.	Age.	Duration of illness.	Previous Roentgen ray therapy.	Original metabolic rate (per cent).	Original pulse rate per minute.
1	Male	42	1 year	None	+29	82
2	Male	43	6 years	None	+54	88
3	Male	43	6½ years	+	+66	88
4	Female	45	1½ years	++	+26	91
5	Male	48	8 months	None	+60	75
6	Male	62	2½ years	+	+31	78
7	Male	65	8 months	None	+41	80
8	Male	67	3 years	++++	+29	88
9	Male	57	1 year	None	+33	70
10	Male	66	6 months	None	+47	80

* + to ++++ indicates extent of previous Roentgen ray therapy.

The earliest specific activity of iodine in chronic lymphatic leukemia was found to be a beneficial effect upon the asthenia and ease of fatigue, and a definite decrease in the state of nervousness and irritability.

The signs and symptoms (profuse sweating, hot flushed skin, tachycardia, nervousness, tremor) which are generally attributed to the increased basal metabolic rate in exophthalmic goiter, are either absent or only slight in patients with leukemia and a similarly elevated basal metabolic rate (Murphy, Means and Aub¹⁹). Minot and Means³⁹ however, are inclined to believe that the similarity in symptoms manifested by both diseases is much more striking. Our own experience, with the present series of patients (*vide supra*), leads us to suspect that the signs and symptoms of chronic lymphatic leukemia are strikingly similar in *quality* to those noted

in exophthalmic goiter, and differ only in a *quantitative* manner, usually being much less intense even in the presence of an equally elevated basal metabolic rate.

TABLE 4.—HEMATOLOGIC DATA IN THE 10 PATIENTS.

Num-ber.	Hemo-globin in per cent (Sahli).	Red blood cells in millions per c.mm.	White blood cells in thousands per c.mm.	Per cent lymphocytes.	Per cent polymorpho-nuclear neutrophils.	Type of lymphocytes.
1	89	4.90	88.9	93	5	Large young cells. No lymphoblasts.
2	40	2.01	102.4	89	9	Young cells with very large nucleus. No lymphoblasts.
3	30	2.00	13.5	59	34*	Primitive cells with blue cytoplasm; but no true lymphoblasts.
4	70	4.58	86.4	96	2	Large young cells. No lymphoblasts.
5	35	2.18	44.8	89	8	Atypical lymphocytes. Nucleus irregular in outline and quite large, almost filling cell.
6	83	4.27	118.0	90	6	Primitive cells with large nuclei and bluish cytoplasm. No lymphoblasts.
7	64	4.16	36.0	83	16	Fragile lymphocytes, some with large nuclei and bluish cytoplasm; others with much cytoplasm and small nuclei.
8	68	3.79	200.0	98	2	Mature lymphocytes with moderate number atypical forms.
9	60	4.12	114.6	99	1	Large young lymphocytes. No lymphoblasts.
10	40	2.48	166.4	98	2	Primitive cells, dark blue cytoplasm.

* Temporary effect following early Roentgen ray treatments.

This observation suggests that these signs and symptoms are not entirely dependent upon the height of the basal metabolic rate in either disease. It seems more probable that the basal metabolic rate and clinical phenomena are dependent in great measure upon a fundamental disturbance which is common to both of them, but which may vary its expression independently under given conditions.

The Iodin Effect in a Goitrous Area. Six of the 10 patients showed a definite and significant decrease in basal metabolic rate, but in only 4 of these did the pulse rate follow this depression (*vide infra*).

The basal metabolic rate in chronic lymphatic leukemia usually begins to fall between the 4th and the 9th day, and reaches its lowest level between the 7th and the 16th day. In 1 patient the initial decrease was delayed until the 14th day.

It is of considerable interest to note that the fall in basal metabolic rate, as well as the period over which this occurs, is directly comparable to similar statistics reported by Means and Richardson,²⁴ and Coller and Potter²⁶ (Table 6) for patients with exophthalmic goiter under treatment with Lugol's solution. It seems of import-

ance, too, to point out that the present series of patients with chronic lymphatic leukemia responded to iodine more nearly like patients with exophthalmic goiter originating in a goitrous region (Coller and Potter²⁶) than like those reported by Means and Richardson²⁴ for a nongoitrous area. The patients with leukemia were all residents of the state of Michigan and were treated under conditions similar to those cases of exophthalmic goiter which were studied by Coller and Potter.²⁶ It is probable that minor discrepancies in the manner of response of these patients to iodine would disappear if the number of cases of leukemia (10) was more comparable to those of exophthalmic goiter (128).

TABLE 5.—THE CLINICAL CHANGES FOLLOWING TREATMENT WITH LUGOL'S SOLUTION.

Number.	Days of treatment.	White blood cells in thousands per cubic millimeter.	Basal metabolic rate in per cent.	Basal pulse rate per minute.
1	0	88.9	+29	82
	11	61.6	+13	64
	31	43.0	+25	68
	35	62.8	+36	80
2	0	102.4	+54	88
	12	49.2	+35	80
	19	30.3	+55	82
	26	72.0
3	0	13.5	+66	88
	5	+68	95
	10	16.8	+34	108
4	0	86.4	+26	91
	14	83.0	+19	88
	23	115.0	+31	88
	29	190.0
5	0	44.8	+60	75
	4	60.6	+20	77
	11	62.8	+35	78
6	0	118.0	+31	72
	15	+10	62
	22	112.0	+4	68
	52	130.0	+52	76
7	0	36.0	+41	80
	9	+49	200*
	14	+43	86

* (Patient developed attacks of paroxysmal tachycardia during basal metabolism.)

8	0	200.0	+29	88
	14	181.0	+33	86
	16	118.0
	17	94.2	+41	88
9	0	114.6	+33	70
	8	70.3
	11	47.8	+39	68
	13	55.3	+35	72
10	0	166.4	+47	80
	8	211.5	+48	89

The following tabulation (Table 6) records the original basal metabolic rates in groups of 10 per cent, and the points to which they decreased following treatment with Lugol's solution. The number of days which elapsed between the former and the latter are also recorded in each instance.

TABLE 6.—THE CHANGES IN METABOLIC RATE DURING TREATMENT.

Original basal metabolic rates in groups of 10 per cent.	Final basal metabolic rates in per cent following iodine in exophthalmic goiter.				Final basal metabolic rates in per cent following iodine in chronic lymphatic leukemia.		
	Means and Richardson (128 cases).	Days.	Coller and Potter (128 cases).	Days.	Present series.	Days.	No. cases.
80 to 90 per cent	+34	10	+38	17	0
70 to 80 "	+24	10	+48	12	0
60 to 70 "	+26	10	+40	14	+26	7	2
50 to 60 "	+24	10	+39	14	+35	12	1
40 to 50 "	+18	9	+30	12	0
30 to 40 "	+15	8	+23	16	+10	16	1
20 to 30 "	+17	8	+17	10	+16	12.5	2

It is quite possible that the widespread and constant use of iodized salt may be one of the factors responsible for the delayed and diminished effect of Lugol's solution in cases from the goitrous areas.

The Basal Pulse Rate. Iodine was effective in reducing the pulse rates of 4 patients, and ineffective in 2 others. It might conceivably have been responsible for a more rapid pulse rate in 4 other patients, one of whom developed repeated attacks of paroxysmal tachycardia. The occurrence of a striking bradycardia, which persisted in the face of an increasing basal metabolic rate, following treatment with Lugol's solution, seemed to be a significant phenomenon.

It has been generally accepted that the elevated basal metabolic rate is directly responsible for the tachycardia with which it is so closely associated, especially in cases of exophthalmic goiter and possibly in the leukemias (Sturgis and Tompkins,⁴⁰ Minot and Means³⁹). Although there is no doubt concerning the relationship which Sturgis and Tompkins have pointed out, those cases which do not follow the general rule suggest that an additional factor may play an important rôle in the tachycardia of exophthalmic goiter, and more especially of chronic lymphatic leukemia.

As a general rule, the pulse rate is well above 90 or 100 per minute in frank cases of exophthalmic goiter with a significantly elevated basal metabolic rate. Only 1 of the 10 patients with chronic lymphatic leukemia showed a basal pulse rate of slightly over 100 per minute, in spite of the fact that 5 of the original basal metabolic rates were recorded between 40 and 65 per cent, 3 rates over 30 per cent, and 2 others about 25 per cent. The combination of a severe anemia, moderate elevation of body temperature and the

possibility of an iodine reaction suggested themselves as possible explanations for this single case of tachycardia.

These observations seem definitely indicative of the fact that the pulse rate is not entirely dependent upon the height of the basal metabolic rate. It is probable, that a disturbance similar to that which causes the elevated basal metabolic rate is also responsible for the tachycardia with which it is often, though not necessarily, associated; and that iodine, while tending to decrease both of them, may have a variable influence.

The Blood Picture. In 4 cases there was an unmistakable decrease in the total white blood cell count, beginning between the 3rd and 9th day, reaching its lowest level about the 20th day, and thereafter gradually increasing to approach its original level after 4 or 5 weeks. In three instances, there seemed to be an actual exacerbation in the numbers of the leukocytes following treatment with Lugol's solution. This took place in spite of the symptomatic remission which was present at the time.

Apparently the decrease, when it does take place, is at the expense of the lymphocytes. Occasionally we have noted the appearance of small numbers of eosinophils and basophils in the peripheral blood stream, following treatment with iodine, but this is not a constant finding.

A marked secondary anemia was present in 7 of the 10 cases which were studied. In three instances, originally without anemia, the red blood cell count and per cent hemoglobin appeared to decrease temporarily following iodine therapy.

It seems of interest to note that iodine therapy appeared to exaggerate the hemorrhagic diathesis which was already present in 1 or 2 of the patients with chronic lymphatic leukemia. Although this association may have been coincidental, it is significant to note that the literature repeatedly mentions potassium iodide as an etiologic factor in hemorrhagic purpura (Ricord,⁴¹ Stengel⁴² (complete bibliography)). Jackson⁴³ has recently called attention to a similar accident in the treatment of exophthalmic goiter with Lugol's solution.

The effect of iodine in reducing the red blood cell count and hemoglobin percentage, and in inducing hemorrhagic manifestations, suggests that this drug may play an important rôle in hemopoietic metabolism.

Regional Lymph Nodes. In 2 cases there was a partial but unmistakable diminution in the size of the cervical lymph nodes bilaterally. The other lymph glands of the body did not show any appreciable changes. Within 2 weeks there was a rapid increase in the size of these cervical glands either in spite of, or because of, the iodine therapy. The significance of this change is uncertain because variations of this type may occur spontaneously (Minot and Isaacs⁴⁴).

Splenomegaly. There were no systematic observations carried out upon the size of the spleen in chronic lymphatic leukemia following treatment with iodine. However, the author has since noted a remarkable decrease in the size of 2 splenomegalies of unknown origin, and a third instance in a patient with chronic myelogenous leukemia, following the administration of Lugol's solution over a period of 1 to 3 weeks. Further observations are now being carried out along this new line of investigation, concerning splenomegalies not due to syphilis or tuberculosis.

The Sympathetic Nervous System. Vasomotor Phenomena. In 2 cases, the patients noted a distinct difference in the skin color, moisture and temperature of their hands before and after treatment with iodine. Originally, both of these patients had complained of pale, cold, rather dry hands, indicative of vasoconstrictor hyperactivity with spasm of the peripheral bloodvessels. Within a few days after treatment was instituted, the palms of the hands changed noticeably, with the appearance of diffuse erythema, slight moisture and increased warmth; and similar changes (not as striking) appeared over the face and ears.

Emotional Instability. A surprising number of patients (8) complained of nervousness and irritability which they had noticed since the onset of their illness. In every case, a marked remission brought definite relief from the emotional instability which they had experienced. In two instances it was only temporary, and was followed within a few days by a definite exacerbation, which later responded favorably to Roentgen ray therapy and transfusion.

Ocular Phenomena. A large number of patients had one or more of the eye signs indicative of a hyperactive sympathetic nervous system,²³ such as, bilateral exophthalmos, unilateral exophthalmos (usually the right eye), lid lag, lidspasm,²³ Kocher and Dalrymple eye signs. It is of interest that unilateral prominence of the eyes and lid lag occasionally decreased following iodine therapy. However, judging from the well-recognized inconstancy of these ocular phenomena,²³ it is uncertain whether or not this was a spontaneous change.

Response to Iodine Controlled by Unknown Factor. Earlier studies upon the effect of Lugol's solution in chronic lymphatic leukemia suggested that severe anemia, previous Roentgen ray therapy and acute exacerbations of the disease acted in an inhibitory manner upon a complete remission. Subsequent investigation, however, has not produced a constant method for predicting the type of response, if any, which one may expect in individual instances.

Conclusions and Summary. The present paper has been designed primarily for the purpose of directing attention to another point of view from which one may regard the clinical phenomena and pathogenesis of exophthalmic goiter and chronic lymphatic leukemia, with special reference to: (a) The mechanism of the elevated basal

metabolic rate in disease; (b) the significance and mechanism of the iodine effect in Graves' syndrome and chronic lymphatic leukemia, and (c) the relation of the sympathetic nervous system to the obvious clinical phenomena of exophthalmic goiter and chronic lymphatic leukemia.

1. The basal metabolic rate may be elevated in many clinical conditions other than exophthalmic goiter (chronic lymphatic and myeloid leukemia, nonleukemic lymphoblastomata, polycythemia vera, pernicious anemia, essential hypertension, acromegaly, diabetes mellitus and convalescent afebrile rheumatic fever). Conversely, all of these maladies, including exophthalmic goiter, may occur without an elevated oxygen consumption.

2. Lugol's solution (iodine) has a definite beneficial effect upon the clinical signs and symptoms of exophthalmic goiter. It also depresses the elevated basal metabolic and pulse rates in pernicious anemia, acromegaly and polycythemia vera. However, iodine has no effect whatsoever upon the basal metabolism and pulse rates of normal individuals, nor does it decrease the elevated basal metabolism and tachycardia of experimental hyperthyroidism induced by active thyroid substance.

3. Ten patients with chronic lymphatic leukemia were systematically studied during treatment with Lugol's iodine solution. Clinical notes were recorded concerning individual variations in clinical symptoms, physical signs and laboratory data. The basal metabolic and pulse rates were studied carefully with special emphasis upon the control period.

4. The basal metabolic rate was found definitely elevated in every patient with chronic lymphatic leukemia, but the initial basal pulse rates were not significantly increased.

5. The physical signs and clinical symptoms of chronic lymphatic leukemia are strikingly similar in *quality* to those noted in exophthalmic goiter, and differ only in a *quantitative* manner. They are usually much less intense in chronic lymphatic leukemia *even in the presence of an equally elevated basal metabolic rate*. These observations indicate that the basal metabolic rate and the other clinical manifestations of these maladies (emotional instability, tachycardia, exophthalmos and associated eye signs, profuse sweating, and vasoconstrictor phenomena) are dependent in great measure upon a fundamental disturbance which is common to all of them; and that the elevated basal metabolic is not responsible for the clinical phenomena of these maladies.

This fundamental disturbance appears to be expressed through a hyperactive state in the sympathetic nervous system, and the resultant phenomena seem to vary independently of each other under conditions which are unknown at the present time.

6. The laws which apparently govern the response of exophthalmic goiter to iodine seem to apply with remarkable similarity to

chronic lymphatic leukemia. However, the percentage frequency of this response in leukemia is smaller than that noted in Graves' syndrome.

7. In a certain percentage of the patients with chronic lymphatic leukemia, iodine will induce a symptomatic remission and a temporary decrease in the basal metabolic and pulse rates, in addition to a transient reduction in the size of the cervical lymph nodes and in the height of the total leukocyte count. It also appears that night sweats may vanish, and certain types of splenomegaly decrease under the influence of iodine therapy.

8. Iodine therapy may, however, exaggerate the hemorrhagic diathesis already present in chronic lymphatic leukemia, and in certain instances induce a decrease in the red blood cell count and hemoglobin. This drug may also cause an exacerbation of those factors (emotional stability, pulse rate, basal metabolic rate and white blood cell count) upon which it sometimes acts in a sedative manner. The mechanism of this paradoxical activity remains unknown.

9. The thyroid gland is not only remarkable for its avidity in storing iodine (Marine and Lenhart⁴⁵), but also for the fact that the epithelial changes in its structural conformation (colloid resting type or hyperplastic and hypertrophic states) may be directly dependent upon the presence or absence of available iodine both in cases of simple endemic and exophthalmic goiter (Marine,⁴⁶ Rienhoff,⁴⁷ Cattell,⁴⁸ Kocher⁴⁹).

One must not confuse this issue by assuming that the activity of the iodine is limited to functions of the thyroid gland, just because the latter is capable of *storing* iodine with unusual facility. Their relationship is probably similar in some respects to that which is known to exist between glycogen and the liver.

Results of the present investigation indicate that the specific beneficial effects of iodine in exophthalmic goiter, chronic lymphatic leukemia, polycythemia vera, acromegaly and pernicious anemia are probably not exerted through the influence of the thyroid gland.

10. One of the most striking effects of iodine in exophthalmic goiter and chronic lymphatic leukemia is its "sedative action" upon the signs and symptoms of sympathetic nervous system hyperactivity (tachycardia, tremor, abnormal sweating, emotional instability, vasomotor phenomena, exophthalmos and associated eye signs). The specific activity of iodine is probably closely related to the physiology of the sympathetic nervous system.

11. The available evidence suggests that exophthalmic goiter is not caused by disease of the thyroid gland. The sympathetic nervous system apparently plays a major rôle in the pathogenesis of Graves' syndrome, and is probably also a factor of importance in chronic lymphatic leukemia.

In evaluating these conclusions, it must be remembered that the

level of the basal metabolic rate is subject to capricious changes. Consequently, the results of the present investigation are of a tentative character from this point of view, and await further and extensive experimentation for confirmation. Nevertheless, there can be little real doubt concerning the beneficial effect of iodine upon the clinical symptoms, and its tendency to decrease the pulse rate and white blood cell count in certain instances of chronic lymphatic leukemia. In any event, the striking clinical parallelism which exists between exophthalmic goiter and chronic lymphatic leukemia is deserving of more critical scrutiny.

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FOOD ALLERGY IN THE DIFFERENTIAL DIAGNOSIS OF ABDOMINAL SYMPTOMS.*

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Food allergy is not infrequently the cause of acute abdominal pain and vomiting and of many other persistent gastrointestinal symptoms.¹ It is indeed probable that such symptoms are the most frequent evidences of food allergy because of the intimate contact that allergy producing foods have with the gastrointestinal membranes. Surgeons as well as internists, therefore, must ever keep food allergy in mind in the differential diagnosis of all abdominal symptoms.

Literature. My attention was first directed to gastrointestinal food allergy by Schloss in 1915² and Cooke³ in 1917. In 1921 to 1923, Duke^{4,5,6} stressed this cause of acute abdominal pain and other symptoms in three contributions. His article on abdominal pain was of special value. In 1925 a study of 234 patients with bronchial asthma allergic indigestion was noted by me⁷ in 12 per cent. In 1927 and 1928 I discussed the rôle of food allergy in the production of abdominal symptoms in 5 articles,^{8,9,10,11,12} in 1 of which¹⁰ 50 cases with such symptoms were reported. Recently, in my book on "Food Allergy,"¹ statistics on 100 patients with gastrointestinal allergy were presented, and an extended discussion of the entire subject with 21 case reports was included. Andresen in 1925¹³ wrote a comprehensive article on gastrointestinal allergy. Eyermann,¹⁴ in 1927, discussed the various gastrointestinal symptoms in allergic patients. Vaughan¹⁵ reported mucous colitis due to food allergy in 1928. In 1930¹⁶ he discussed the rôle of food allergy

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in abdominal as well as general symptoms. Balyeat,¹⁷ in 1930, also emphasized gastrointestinal food allergy. Charles Richet, who coined the word anaphylaxis in 1902, was one of the first to describe gastrointestinal symptoms due to food allergy and his views were presented by Barnathan¹⁸ in a thesis on the subject in 1911 and again by Laroche, Richet and Saint Girons¹⁹ in 1919. These contributions, as well as those of Schloss,²⁰ described the various gastrointestinal symptoms of food allergy in childhood. Recently, in 1931, Stafford, Jacobus and Watson²¹ again discussed these manifestations in childhood.

Clinical Observations. In my recent discussion of gastrointestinal food allergy²² an analysis of 50 of the records of a series of 100 patients with such disorders revealed the occurrence of the following symptoms:

Canker sores, 20 per cent; coated tongue, 18 per cent; heavy breath, 14 per cent; distention, 32 per cent; belching, 20 per cent; sour stomach, 18 per cent; epigastric heaviness, 28 per cent; burning or pyrosis, 14 per cent; nausea, 40 per cent; vomiting, 30 per cent; intestinal cramping, 24 per cent; mucous colitis, 14 per cent; diarrhea, 12 per cent; constipation, 32 per cent; proctitis, 2 per cent; pruritus ani, 4 per cent; pain and soreness in the epigastrium, 20 per cent; in the upper right quadrant, 14 per cent; in the mid-abdomen, 10 per cent; in the lower abdomen, 20 per cent, and an ulcer type of pain, 10 per cent. Symptoms including weakness, fatigue, irritability, nervousness, mental dullness and confusion and generalized aching due to "allergic toxemia" from food were present in a number of these patients. All of the above symptoms have been found in another series of 150 patients, statistics of which have recently been published.¹ My findings are quite like those reported by Eyermann¹⁴ in 1927. A family history of allergy was present in 65 per cent of the patients and a personal history of asthma, hay fever, cutaneous allergy or migraine was present in from 13 per cent to 36 per cent. My studies²³ indicate that allergic patients often inherit the tendency to develop a specific type of allergy such as food or pollen allergy as well as a specific localization of its manifestations such as hay fever or migraine. Thus it is interesting that patients with gastrointestinal allergy often give a history of chronic abdominal disturbances in their forebears which resemble those of the patient."

It is also interesting that Lintz states in 1925²⁴ that a family history of chronic appendicitis should suggest allergy rather than infection as the underlying cause. It must be emphasized, however, that certain patients with gastrointestinal and other manifestations of allergy have no personal or family history of allergy.

Gastrointestinal Food Allergy from the Surgeon's Viewpoint. Special comment on the various manifestations of gastrointestinal food allergy is important in order to indicate the necessity of the constant

consideration of this etiologic factor in differential diagnosis. Acute as well as mild and chronic manifestations will be discussed in this paper. It is well to remember that allergy produces two main reactions in tissues which give rise to its symptoms—first, edema of mucous membranes and other tissues with the concomitant production of mucus and disturbed membrane permeability, and second, smooth muscle spasm which may occur in any tissue containing such smooth muscle from the bronchi or arteries to the gastrointestinal or urogenital tracts. The mucous membranes and the abundant smooth muscle of the digestive tract, therefore, are natural sites for the establishment of allergic reactions from foods. It is probable that lesions similar to urticaria, erythema and even eczema in the skin may occur in the various parts of the gastrointestinal tract. Angioneurotic edema has been observed at operation for supposed obstruction.²⁵

It is likely that allergic reactions to bacteria and other allergens than food may produce symptoms in various parts of the gastrointestinal tract. Pollen allergy has produced symptoms in a few of my patients as well as patients of other observers.²⁶ However, food is the outstanding cause of allergic digestive symptoms and our discussion will be confined to such etiology.

1. GASTRIC SYMPTOMS. I have reported food allergy as a frequent cause of distention, belching, pyrosis, epigastric heaviness, nausea, vomiting and sour stomach. Such symptoms may be mild or severe and may occur immediately or be delayed for 1 to 3 hours. The digestive disturbances and especially definite food intolerances in infancy are frequently due to food allergy and it is probable that many cases of pylorospasm are due to allergic edema and smooth muscle contraction. The frequency of canker sores, white coatings on the membranes of the mouth and gums, and coated tongues in patients with abdominal allergy deserves mention at this place. The possible relation of canker sores to peptic ulcer will be discussed later. The gastrointestinal symptoms so frequently associated with migraine have been relieved through my "elimination diets." It is my opinion²⁷ as well as that of Balyeat²⁸ that most cases of migraine are due to food allergy.

2. INTESTINAL SYMPTOMS, VOMITING AND ANOREXIA. It is probable that nausea due to food allergy may arise in certain patients from disturbed peristalsis in the small intestine or in the stomach. Colic, cramping, abdominal pain and mucous colitis may be due to similar reactions. My Roentgen ray studies of certain patients²⁹ with gastrointestinal allergy have revealed moderate duodenal stasis and reversal of peristalsis as well as hyperperistalsis and hypermotility, which apparently depended on the inclusion of allergy-producing foods in their diets. Further Roentgen ray studies on the small intestine in patients with gastrointestinal allergy are in progress.

3. COLONIC SYMPTOMS. The spasm and mucus of mucous colitis can well be explained by food allergy. Such etiology has been reported by Duke⁴ in 1921, Vaughan³⁰ in 1922 and 1928, Richet³¹ in 1926, Hollander³² in 1927, the writer in 1928, Beecher³³ in 1928 and Balyeat¹⁷ in 1930. Pain, soreness and disturbed peristalsis are at times due to this condition which may not be readily recognized. I have discussed mucous colitis³⁴ in my recent monograph, and case reports have been included. It is probable that the so-called irritable bowel for which no satisfactory etiology has ever been presented often may be due to food allergy.³⁵ Many of my patients affected with food allergy have suffered with colonic pain and tenderness and other symptoms characteristic of the irritable bowel. Right-sided abdominal pain³⁶ and soreness due to allergic reactions in the ascending colon occur frequently and will be referred to later. Disturbances in the harmonic peristalsis in the colon due to food sensitizations as observed in the Roentgen ray have been described by Eyermann.¹⁴ Pruritus ani due to food allergy was described by Andresen in 1925.¹³ In 1928¹⁰ I reported such etiology and Vaughan¹⁶ in 1930 reported several cases. Pruritus ani due to allergy is an example of the usual tendency to the localization of allergic reactions. Idiopathic bleeding from the intestinal tract has been described by Lintz.³⁷ Other idiopathic hemorrhages in allergic patients have been discussed in my recent book.³⁸ Finally, food allergy has been a frequent cause of constipation in my patients due to spasm in the colonic musculature.

4. ABDOMINAL PAIN AND SORENESS. The cause of abdominal pain and soreness is a constant challenge to every surgeon and physician. Food allergy is a frequent cause of these symptoms and must always be considered in the differential diagnosis.

(a) Abdominal pain suggesting appendiceal inflammation may be due to food allergy. It is not surprising that the ascending colon and especially the cecum are frequently the seats of reactions due to food allergy since the food residues remain in contact with these tissues for many hours in normal patients.

Allergic reactions in the cecum probably extend into the appendix as well and it is entirely probable that the resulting edema and spasm may predispose to infection. As already stated, Lintz²⁴ feels that many appendectomies are done because of allergic reactions in the colon and appendix. My experience also shows that pain and soreness in this region may be due to allergy alone. Acute allergic³⁹ reactions moreover may be accompanied by fever, a leukocytosis of 12 to 20,000, though the polymorphonuclears are usually below 80 per cent. Many so-called cases of chronic appendicitis are also probably due to food allergy. Allergic reactions in the appendix and cecum may predispose to bacterial invasion, especially when resistance to such infections is naturally low or diminished. When definite rigidity is present, however, and other indications of an

acute appendicitis are found surgery should never be postponed even when allergy is suspected.

(b) Abdominal pain and soreness suggesting gall bladder disease may also be due to food allergy. Allergic pain in the upper right quadrant is usually dull, though it is at times severe. There is frequently a rather constant pain and soreness in this area and over the whole region of the liver, such as I reported in 12 patients in 1928¹⁰ due to food allergy. Severe pain suggestive of gall-stone colic has not been observed in my work. The whole right side of the abdomen may be affected. Graham, Cole, Copher and Moore⁴⁰ have reported similar observations of Alexander and Eyermann. They list intestinal allergy as a third consideration in their differential diagnosis of cholecystitis. As I have recently stated, it is probable that allergic reactions occur in the liver itself. Patients with chronic food allergy, especially those with severe "bilious headaches," are at times moderately jaundiced, indicating swelling of the parenchyma of the liver with edema or spasm of its ducts. Other evidence in favor of hepatic allergy has been reviewed elsewhere.⁴¹ Pain and soreness in the upper right quadrant may also be due to colonic reactions as reported by Eyermann and observed in my own studies and it must be mentioned that Duke⁴² and I have reported renal colic due to food allergy.⁴³ Thus pain and soreness in the upper right quadrant, especially in a patient with active or potential allergy should suggest food allergy as a possible cause.

(c) Abdominal pain suggesting peptic ulcer may be due to food allergy. Such pain occurred in 5 patients as recently reported in my series of 50.⁴⁴ In 1 of these patients, in whom a provisional diagnosis of ulcer was made some years before, an unnecessary exploratory operation was performed because of sudden severe pain, which was attributed to possible perforation. Since then his pain has been shown to be due to wheat allergy.

The association of food allergy and peptic ulcer has come to my attention several times. Carr,⁴⁵ in 1926, reported milk allergy in a patient with ulcer, in whom severe headache, nausea, drowsiness, urticaria, tender painful joints and a temperature of 101.2° F. developed whenever he was placed on a milk régime. Sterling, in 1929,⁴⁶ reported 2 such cases and I have recently recorded 2 others.⁴⁷ Kern and Stewart⁶² have recently reported on the incidence and significance of food hypersensitiveness as observed in 32 patients with duodenal ulcer.

I have stated in 1928¹⁰ and again in 1931⁴⁸ that canker sores are frequently due to food allergy. Andresen, in 1925,¹³ affirmed such etiology. I have also suggested that lesions similar to canker sores could readily occur in the stomach or duodenum and that the continued action of the digestive ferments on such sores could produce peptic ulcers of varying degrees. This possibility is receiving further study.

(d) Abdominal pain and soreness due to food allergy may occur in other parts of the abdomen than those already discussed. Such symptoms in the upper left abdomen have been observed in 4 patients,⁴⁹ probably due to colonic reactions. Mid-abdominal and left-sided pain may also occur. Three patients with recurrent severe attacks of pain localized in a small area to the left and just below the umbilicus in whom food allergy was the sole cause have been reported.⁴⁹

Pain in the lower abdomen may be due to food allergy localized in the descending colon or sigmoid or small bowel. Rectal spasm and tenesmus with pain referred to the back is not infrequently due to food allergy. Lower abdominal pain and soreness may be due to bladder⁵⁰ or uterine allergy,⁵¹ producing painful burning urination and painful disordered menstruation.

Angioneurotic edema may cause severe abdominal pain and signs of intestinal obstruction as I have previously reported. Such lesions have been discovered at exploratory operations. Osler,⁵² in several articles, warned against surgery in patients with visceral manifestations of the erythema group of skin diseases, and in 1914⁵³ he predicted that anaphylaxis would probably explain such symptoms. Food allergy has been shown by Alexander and Eyermann⁵⁴ to be a definite cause of Henoch's purpura and angioneurotic edema is frequently due to food allergy in my experience and that of other students of the subject. As a cause of acute or severe abdominal pain, therefore, food allergy must be kept in mind by all surgeons in order to prevent unnecessary operative procedures. This is especially true when physical findings do not correspond with the degree of severity of the presenting symptoms. Many exploratory operations with negative findings have been done because of allergic symptoms.

Diagnosis. Before outlining the various criteria which should direct the physician's attention to the possibility of food allergy in his patient, it must be emphasized that complete and painstaking physical and laboratory examinations must be done to determine all types of existing lesions. This is most important before food allergy as a cause of the various symptoms which have been discussed in this paper can be definitely considered. Such studies should include a careful history and physical examination, a stomach analysis, stool analyses, Roentgen ray studies of the gastrointestinal tract of the colon by means of a barium enema and gall bladder studies preferably with the intravenous dye. Proctoscopic examinations and other laboratory studies should be done when indicated. I have recently discussed the importance in Roentgen ray studies of a menstruum for barium to which the patient is not allergic. The use of milk in patients sensitive to it produces peristaltic disturbances which may confuse the roentgenologist.

The presence of definite lesions in the gastrointestinal and biliary tracts does not rule out the presence of food allergy. This was stressed by Duke⁴² and I can corroborate his opinion. As already stated, allergic reactions may predispose to appendicitis, cholecystitis and initiate peptic ulcer. Thus it is necessary at times to carry out surgical or medical therapy for definite pathologic conditions as well as modify the diet to control food sensitizations.

What should make the physician suspect allergy in his patient?

1. A personal or family history of asthma, hay fever, urticaria, eczema, migraine or of recurrent colds or coughs and in certain instances of chronic gastrointestinal symptoms should suggest potential allergy in the patient. I have repeatedly stated that the general history of every patient studied by physicians should offer evidence that careful questioning for such potential or active allergy has been made. Possible allergy of all types including food allergy is extremely common, as shown by my recent analysis⁵⁶ of 400 college students in whom potential allergy was present in 58 per cent.

2. The history of definite food disagreements and dislikes should suggest the possibility of allergy. Here the rôle of inadequate digestion and nervousness must be kept in mind, but allergy is more often indicated by such history than is appreciated.

3. Skin testing with foods should be done. I have stressed for several years the frequency of negative cutaneous, and to a definite though less extent, of negative intradermal reactions to food allergens to which sensitization exists. The necessity of diet trial has been emphasized by me as well as by Brown,⁵⁷ Alexander⁵⁸ and Eyer-mann⁵⁹ where negative as well as positive skin reactions occur. These negative reactions depend on the localization of the allergic disturbances in the special tissues rather than in the skin, as pointed out by Alexander⁶⁰ in 1928. My continued experience indicates that skin reactions should be carried out when possible, though they are rarely of much help in the study of patients with gastrointestinal allergy.

The determination of food allergy, therefore, must be made with diet trial. For this my "elimination diets" have been of increasing service. Many obscure symptoms have been found due to food allergy by means of these diagnostic diets. Treatment of food allergy requires a gradual development of such "elimination diets" with the gradual determination of the specific foods which are productive of the symptoms. Desensitization to such foods may result from their prolonged elimination from the diet or may be accomplished by gradual feeding.

Summary. 1. Many gastrointestinal symptoms have been discussed which may be due to food allergy.

2. The realization that food allergy can produce a wide variety

of gastrointestinal symptoms necessitates the consideration of this etiology in the differential diagnosis of abdominal complaints.

3. These symptoms frequently simulate acute or chronic abdominal lesions and have led to many unnecessary operations in the past.

4. The necessity for the study of every patient with potential or active allergy in mind is paramount. Positive or negative evidence of such allergy should be included in the family and personal history of every patient.

5. Because of the frequency of negative skin reactions in food allergy the use of "elimination diets" for diagnosis has been found of increasing value.

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SYPHILITIC ARTHRITIS WITH EFFUSION.

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THE literature can be summarized in the following sentence: Syphilitic arthritis can imitate every form of joint disease. Finger,¹ Frauenthal,² Hartung,³ Schlesinger,⁴ Todd⁵ and others recognize acute febrile affections, resembling infectious arthritis; subacute forms simulating rheumatoid (atrophic) arthritis; chronic types with the clinical appearance of (hypertrophic) osteoarthritis. The affection can be monoarticular, symmetrical or polyarticular. The intensity of involvement varies from simple effusion to gummatous granulation and finally to destructive processes of the membrane and articular surface with deformity and ankylosis. The diagnosis is based on peculiar clinical features, response to treatment, Roentgen ray findings and the Wassermann reaction in blood serum and joint fluid.

The evidence, however, is at best sufficient to identify only a fraction of the types enumerated above. The pathologic foundation is inadequate, consisting of a limited number of older descriptions of gross specimens demonstrating gummatous involvement or chondritis (Lancreau,⁶ Virchow,⁷ Gangolphe,⁸ Gies,⁹ Chiari,¹⁰ Kaufmann,¹¹ Schmidt¹²). Only a few microscopic studies were reported.

The estimation of frequency also is subject to extreme variations. Stein¹³ calculated syphilitic arthritis to amount to 20 per cent of all forms; Brunauer and Hass,¹⁴ to 2 per cent of their material. The elusive and complex clinical description, the discrepancies and difficulties of detection have had the result that the whole subject was almost lost sight of. The impression is prevalent, that tabetic arthropathy is the only manifestation of syphilitic joint disease. This is liable to cause grave consequences, as syphilitic arthritis often yields to proper treatment only, if recognized in an early stage. Reinvestigations are indicated to clarify and to amplify our knowledge of syphilitic arthritis. It is thought that this can be accomplished by the analysis of well-defined forms on the basis of a broad material. My study is devoted to a consideration of the type of syphilitic arthritis with effusion as the main clinical feature. This permits one to base the diagnosis by correlation of clinical findings with the findings in the joint fluids and to consider this type of syphilitic arthritis as a sector of the whole group of arthritides with effusion.

Analysis of the Material. The material for this investigation consists of 112 cases of acute and chronic arthritis with effusions of various etiology. The details will be found in Table 1. Nine

cases were diagnosed as syphilitic arthritis; seven cases of simple synovitis; the 8th is combined with a juxta-articular gumma; the 9th is a case of synovitis with osteochondritis and periostitis. In addition we shall discuss a case of synovitis with gumma at the articular surface of the femur and 2 cases of tabetic arthropathy not included in this series.

TABLE 1.—DIFFERENTIAL DIAGNOSIS OF 112 CASES OF ARTHRITIS WITH EFFUSION.

Etiology.	Acute and subacute.		Chronic.		All forms.	
	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.
"Nonspecific"	35	31.0	49	44.0	84	75.0
Doubtful	1	0.9	5	4.4	6	5.3
Tuberculous	1	0.9	4	3.6	5	4.4
Gonorrheal	6	5.4	1	0.9	7	6.3
Tabetic	0	..	1	0.9	1	0.9
Luetic	4	3.6	5	4.4	9	8.1
Total	47	41.8	65	58.2	112	100.0*

* Percentages carried out to tenths only.

A. SYPHILITIC SYNOVITIS.

Case Reports. CASE 1.—V. K., girl aged 6 years. Her mother had miscarriages before and after the child's birth and her blood Wassermann was strongly positive. Three months before admission to the Clinic the child developed a bilateral eye condition, which was diagnosed as parenchymatous keratitis. Wassermann and Kahn tests were 4+ in the blood. She received 6 injections of arsphenamin. During treatment and 2 weeks before entering the Clinic, she developed swelling of both knees, almost painless. Each knee was distended, especially over the suprapatellar bursa. There was no marked increase of temperature or thickening of the synovial capsule. Twenty cubic centimeters of a slightly cloudy, greenish fluid were aspirated from the left knee joint. It contained a dense fibrinous net. The Wassermann was 4+ in the joint fluid and in the blood. Roentgen ray was negative. For other findings see Table 2. The patient continued the antiluetic treatment with the addition of mercury inunctions. One month later the swelling disappeared and the Wassermann in the blood returned to negative. Check-up examination in 3 months showed a normal condition of the joints.

CASE 2.—C. I., boy aged 8 years. His mother stated that 6 weeks previously the child fell and subsequently developed pain and swelling of the left knee. On examination the child was walking with a limp and the left knee joint was tender and swollen (increase of $1\frac{1}{4}$ inches in size over the right knee). Extension was limited to 160 degrees and flexion to 45 degrees. The temperature over the joint was somewhat increased. The Roentgen-ray showed effusion but no atrophy or destruction. Plaster was applied for 8 days, after which strapping was done, but the condition remained unchanged. Tuberculosis was suspected and the case was referred for aspiration by Dr. M. Herzmark. Twenty cubic centimeters of a pale turbid fluid were recovered. The Wassermann was 4+ in the fluid and blood. For other tests see Table 2. The mother denied venereal infection and her Wassermann was negative. The patient was given mercury ointment locally and injections of bismuth and the swelling subsided within a month. Check up after 8 months showed that the knee remained normal and the blood Wassermann negative.

CASE 3.—D. B., girl, aged 4 years. Her mother stated that the child fell a week previously and developed a swelling of the right knee. The child is normally developed and there were no signs of congenital lues. The tonsils were enlarged and the throat inflamed. The knee was swollen and the central cavity and the suprapatellar bursa were distended with fluid. Only slight limitation of motion existed and there was no increase of local temperature. The Roentgen ray was negative. Thirty cubic centimeters of a pale turbid fluid were aspirated. The Wassermann was 4+ in the joint fluid and the blood. See Table 2 for other findings. The mother had one miscarriage previous to the birth of the child but declined a Wassermann test. Patient was given local inunctions of mercury and referred for general antiluetic treatment. However, this was not carried out and the patient returned after 2 months with the condition unchanged. The right knee was reaspirated and 20 cc. of fluid of the same character were obtained, which again gave a 4+ Wassermann. The patient again failed to carry out the antiluetic treatment for 4 weeks, when she finally returned with swelling and fluctuation of both knees. After 2 injections of bismuth, the right knee improved; however there was increased pain and swelling of the left knee. The patient is still under treatment.

CASE 4.—E. B., colored girl, aged 20 years. She complained of swelling of the right knee since childhood. At the age of 13 the leg was put in a plaster of Paris cast for 4 months; again in 1927 a cast was applied for 9 months. At that time there was also swelling of the left ankle. There was no improvement by the treatment. Since February, 1930, she attended the night Clinic here and was treated with diathermia and massage. The Wassermann in the blood was strongly positive at that time but only physiotherapy was given until September, 1930. The patient was in good general condition. She had strabismus and defective teeth. There were no signs of congenital lues. The right knee was greatly enlarged, the capsule and ligament appearing to be hypotonic. She had marked knock knees. One hundred and twenty cubic centimeters of a greenish, slightly cloudy pale fluid were aspirated on which the Wassermann was 4+. For other findings see Table 2. Mercury was given locally with arsphenamin and bismuth injections. Within 3 months a complete resorption of fluid took place and a check up showed a normal knee after 4 months.

CASE 5.—B. R., colored woman, aged 24 years. She complained of pain and swelling of the right knee for 3 years. She denied knowledge of luetic infection. Her general condition was fairly good but she was constipated. Teeth and tonsils were all right. There was moderate hydrocephalic formation of the skull. She gave no history of serious disease of operation, and denied knowledge of syphilitic infection. The right knee joint was swollen and slightly tender and fluctuated chiefly in the suprapatellar pouch. There was no increase in local temperature. The patient walked without a limp. One hundred and twenty cubic centimeters of a thin, greenish, noncoagulating fluid were aspirated. The Wassermann was 3 to 4+ in the blood and fluid. The Roentgen ray was negative. She was given local mercury ointment and referred for general antiluetic treatment. Due to a misunderstanding she did not appear for the general treatment. She returned a month later, however, with a reaccumulation of fluid and 40 cc. of a turbid, yellow fluid were aspirated. The Wassermann was 2+. For other results see Table 2. The patient was then given 2 injections of novasurol. Gingivitis and uterine hemorrhages appeared; however, the knee joint returned to normal and the blood Wassermann was negative. Check-up examination 2 months later showed a normal knee.

CASE 6.—P., mechanic, aged 38 years, is married, has 2 healthy children. He denied syphilitic infection. Eight months previously he arose suddenly from a chair and felt a snap in the right knee joint, followed by a swelling.

TABLE 2.—FINDINGS IN JOINT FLUIDS IN 10 CASES OF SYPHILITIC ARTHRITIS.*

Case No.	Name.	Age.	Duration.	Diagnosis.	Positive Wassermann.		Cell count.	Neutrophils, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Synovial cells per cent.	Guinea-pig inoculation.	Icterus index.	Remarks.
					Blood	Fluid.								
1.	V. K.	6	2 wks.	Synovitis, bilateral knees	4	4	...	66	22	12	0	Not done	3.8	Parenchymatous keratitis 6 weeks before arthritis onset; first aspiration, left knee; second, right knee.
	V. K.		Second aspiration, 1 week later		4	4	18,300	76	16	8	Few	Not done	3.6	Blood admixed.
2.	C. I.	8	11 wks.	Synovitis, left knee	4	4	80	5	15	Negative	15.0	
3.	D. B.	4	1 wk.	Synovitis, left knee	4	4	22,500	90	10	Negative	2.0	
	D. B.		Second aspiration 6 weeks later		4	4	5,000	64	28	8	..	Negative	2.4	
4.	E. B.	20	14 yrs.	Synovitis, right knee	4	4	5,450	Few	25	40	35	Not done	2.5	
5.	B. R.	25	2 yrs.	Synovitis, right knee	4	3	4,000	20	68	8	4	Negative	2.4	
6.	H. P.	38	8 mos.	Synovitis, right knee†	4	4	500	10	70	15	5	Not done	3.2	Hemorrhagic fluid was aspirated from suprapatellar bursa.
7.	B. E.	45	2 mos.	Synovitis, right knee	4	4	250	10	85	0	5	Negative	2.1	
8.	J. P.	40	6 mos.	Synovitis with joint gumma, left knee	2	2	23,000	84	8	8	0	Negative	2.8	Aspiration after operation.
9.	I. D.	8	2 wks.	Osteochondritis, left knee	4	4	10,300	18	52	20	10	Negative	2.8	
	I. D.		Second aspiration		4	3	5,600	60	20	10	20	Negative	Not done	
10.	K. A.	27	2 yrs.	Gummatous arthritis, left knee	4	4	...	4	81	0	15	Not done	4.0	Ankylosis of left elbow for 3 years.

* Cultures negative in all cases.

† Fluid from popliteal bursa.

The condition persisted in spite of physiotherapy. There was no pain and the patient continued working. He was in good general condition and had had no other serious illness. There were no signs of rheumatic disturbances, nor remnants of luetic infection with the exception of a hydrocephalus and 2 hard nodes over the shafts of the tibia in about the middle of the leg. Roentgen ray showed congenital tubercles of the tibia. The right knee joint was irregularly extended by a bulging in front due to accumulation of fluid in the suprapatellar bursa and a large swelling of the posterior aspect, due to fluid in the popliteal bursa. Both cavities were aspirated by Dr. Saschin. The fluid from the suprapatellar bursa was slightly hemorrhagic. However, as the fluid was not examined until the next day, it cannot be definitely stated whether the blood was not admixed during aspiration. Thirty cubic centimeters of a very pale, thin, only slightly turbid fluid were aspirated from the popliteal bursa. The Wassermann was 4+ in both joint fluid and blood. See Table 2 for other results. The patient was given local inunctions and was advised to take general antiluetic treatment. This he neglected for 4 weeks; at the end of which time he still had swellings, especially of the popliteal bursa. Under antiluetic treatment the swelling disappeared entirely from the suprapatellar and popliteal bursæ.

CASE 7.—B. E., laborer, aged 45 years, denied knowledge of venereal disease. For 1 month he had had swelling and pain of the right knee joint and was treated with diathermia and massage without effect. One month later 60 cc. of fluid was aspirated by Dr. D. Sloane. The Wassermann reaction was 4+ in both joint fluid and blood. For other findings see Table 2. The patient was given mercury ointment and general antiluetic treatment. Two months later the knee was practically normal. Seven months later there was recurrence of the effusion which quickly subsided under physiotherapy. The Wassermann was negative.

Analysis. This group represents a late stage of syphilitic infection. Congenital lues may be assumed in the first 4 cases; 3 being children; the joint affection in the 4th dates back to the age of 6 years. The date of infection cannot be ascertained in the remaining 3 cases. The onset was recent in 4 cases (1 week to 2 months' duration), and chronic in 3 cases (8 months to 14 years). The symptomatology is uniform, consisting chiefly of an effusion of the knee joint, bilateral in the first case and unilateral in the rest. In Case 3, effusion developed in the unaffected knee in the course of treatment. The process is almost entirely confined to an inflammation of the synovial membrane. Even the very chronic cases do not present signs of involvement of other joint structure; there is no periarticular thickening nor muscle contracture. The Roentgen ray does not reveal atrophy or destructive or productive changes at the articular surface or metaphysis. For this reason, pain is very moderate; active and passive motion and weight bearing are not markedly limited. Systemic reactions were absent; the temperature was normal; local heat was only slightly raised in the recent cases. The process is eminently stationary, not amenable to nonspecific treatment but still limited to the synovial membrane after years duration.

Diagnosis. First the presence of syphilis and second the syphilitic etiology of the joint affection have to be proven. The history of

infection was negative in this group. However, in 2 cases the mothers had admitted miscarriages, 1 of them having a strongly positive Wassermann. Other signs or remnants of syphilis were missing with the exception of a syphilitic keratitis in the first case. The Wassermann reaction was strongly positive in the blood serum and joint fluids. The diagnosis of syphilis is therefore almost entirely based on serologic evidence. This is sufficient, none of the complications being present which are liable to produce nonspecific reactions.

The second task, the proof of the syphilitic origin of the synovitis, is far more complicated. Jacket and Durand,¹⁵ Reschke,¹⁶ Brunauer and Hess,¹⁴ Schlesinger,⁴ Todd,⁵ Hoffmann¹⁷ and others found that the Wassermann reaction in the joint fluid was often positive while the reaction in the blood serum was negative. This would indicate a local production of specific antibodies and prove the syphilitic etiology of an effusion. However, the number of cases is limited and the authors did not give details of the technique. Poehlmann,¹⁸ in a careful study, found that the Wassermann reactions in the joint fluids were positive only when the blood was likewise positive.

My own studies¹⁹ and a recent investigation with Dr. Pinkus²⁰ on the Wassermann reaction in 150 fluids corroborated and amplified these results. It should be emphasized that nonspecific reactions are likely to occur in joint fluids unless a rigid technique is followed. On the basis of these studies we do not accept a positive Wassermann reaction in joint fluids as conclusive proof of the syphilitic nature of the synovitis. However, it is of value as a link in the chain of evidence which is reached by complete examination of the joint fluids, consisting of cultures, gonococcus complement fixation tests, guinea-pig inoculations and cultures for tuberculosis. Positive results of these tests are regarded as evidence against the syphilitic etiology of the arthritis. A negative Wassermann reaction in the joint fluid of a known syphilitic is by itself a proof of the nonsyphilitic etiology of the arthritis.

A positive Wassermann reaction with otherwise negative findings in the joint fluids carries considerable weight in favor of the specific etiology. However, the final decision is still reserved until the progress and therapeutic response confirm the diagnosis.

Interpretation of weakly positive Wassermann reactions must be still more guarded in a case in which infection is denied and other manifestations of lues are absent. Control examinations have to be carried out in the blood and fluid to ascertain the stability of these weak reactions and a prolonged nonspecific treatment should first be given. The failure of this procedure and the success of subsequent antiluetic treatment is the final indication of the significance of the weak Wassermann reactions.

Of other findings in the effusion, the cell count studies do not give differential diagnostic clues. In recent cases the cell count was found to be high, going to 23,000 cells per c.mm., and the polymor-

phonuclears prevailed (up to 90 per cent). In chronic cases the total of cells is low (250 per c.mm.); the polymorphonuclears decrease and the monocytes rise (as high as 90 per cent). In 2 cases the number of synovial cells reached 20 and 35 per cent respectively which, according to my studies,²¹ indicates hypertrophic changes of the synovial membrane.

The effusions did contain products derived from the circulation as well as from the hypersecretion of the synovial membrane. This is proven by a peculiar precipitation phenomenon, consisting in the formation of a sack or closed membrane, if a drop of the synovial fluid is let fall into a test tube of diluted acetic or hydrochloric acid. This test and its bearing on the origin of inflammatory effusions is discussed elsewhere.²²

The importance of bilirubin estimation in the joint fluids will be pointed out in connection with the clinical aspects.

Pathologic evidence is deficient, as in any other form of synovitis. It is not to be expected that the histologic examination will always clinch the diagnosis, because syphilis produces, besides specific *granuloma*, nonspecific inflammatory pictures. This is brought out by the following reports: Schuchard²³ found in an acute case of syphilitic synovitis, miliary gummata in the subsynovia. Borchard²⁴ published a case of villus synovitis with gummata. Bosse²⁵ did an exploratory excision of the synovial membrane in 3 cases and found a granulation tissue in 2 and gumma with giant cells and necrosis in 1 case of hereditary syphilitic arthritis. Bering²⁶ as well as Hoffmann¹⁷ examined a synovial membrane in 1 case each, finding only nonspecific inflammatory changes. Chesney, Kemp and Baetjer²⁷ produced syphilitic orchitis in rabbits by injecting joint fluids from 3 cases of luetic arthritis. Unfortunately the experiment was not carried out simultaneously with blood studies; these patients being in the early secondary stage, the possibility that the spirocheta were carried into the fluid from the blood stream is not excluded.

Clinical Consideration. History of trauma was given in 4 patients. That injury was not the direct cause of the effusions is proven by the examination of the fluids. Recent traumatic effusions are hemorrhagic; older effusions have a high icteric index (as pointed out in my recent study on the bilirubin content of synovial fluids²⁸). Only once a hemorrhagic fluid was obtained from the suprapatellar bursa; even in this case fluid from the popliteal pouch was free of blood. Therefore, admixture of blood during aspiration must be considered. The icterus index was low, with the exception of 1 case. On the other hand it is well known and confirmed by recent investigation (Michael²⁹) that trivial injury may provoke syphilitic manifestations, especially in the late stages of lues. The discrepancy between the history of injury and the inflammatory character of the effusion contributes, therefore, affirmative evidence.

The onset of the synovitis occurred in 4 cases (57 per cent) between the ages of 4 and 8 years. This is significant, as in our material, children up to 14 years amounted to only 10 per cent of the total. In children syphilis is, next to tuberculosis, the most frequent cause of uni- or bilateral arthritis of the knee joints.

Evidence of focal infection was only present in Case 3 where there was a tonsillitis. However, onset after slight trauma, absence of temperature, location, character of the effusion and response to treatment are against a septic or toxic etiology of the synovitis in this syphilitic child.

Therapeutic Evidence. The failure of nonspecific measures in this groups of synovitis is very suggestive. In 5 cases (Nos. 2, 4, 5, 6, 7) internal medication, local applications, physiotherapy, or plaster casts were applied without improvement. The effect of antiluetic treatment is the oldest evidence of the syphilitic nature of a given case of arthritis. James Russel,³⁰ as early as 1802 recognized venereal contamination as the cause of "one form of symptomatic dropsical swelling of the knee joint, in which the most powerful generic remedies are of no avail, unless the specific disease be first removed by a complete course of mercury." He also made the observation that recurrences happen and it is necessary to continue the treatment until the venereal disease is eradicated. The etiologic evidence is based on the reaction during the course of treatment as well as on the final result.

At the beginning of the treatment either no change nor exacerbation of the symptoms occurred. Of special interest is the first case, which developed the bilateral effusion of the knee joints during a course of antiluetic treatment. This is evidently a Herxheimer reaction, due either to liberated endotoxins or to the effect of the drugs on hypersensitized tissues. The same reaction appears to be responsible for the involvement of the left knee in Case 3 during the treatment. As long as the dosage is insufficient no marked improvement takes place. This is well illustrated in 3 cases (Nos. 3, 5, 6) where the application of energetic treatment was delayed for several months. The effect of the treatment in the intermediary stage can often be demonstrated by the decrease of the strength of the positive Wassermann reaction in the fluids. A full course of treatment is necessary to produce resorption of the effusion, and cure. This result was obtained in 6 cases, the 7th still being under treatment.

Such interpretation of the effect of the treatment eliminates the objections that some of the antiluetic drugs, especially iodids, are efficient also in nonspecific arthritis. Our cases did not receive iodids at all and this drug is not an antiluetic in the strict sense of the word. Iodids are further effective chiefly in the hypertrophic type of arthritis developing past middle age. No evidence was produced that it is of value in simple synovitis. We are inclined to consider the cure of an arthritis in a syphilitic, after insufficient doses of

specific treatment, rather as evidence against the syphilitic nature of the joint involvement. A failure of energetic and prolonged anti-luetic treatment in this group, where the process is limited to the synovial membrane, should also be regarded as an indication of a different etiology of the synovitis. If therefore, a latent syphilitic, who has undergone full courses of treatment and is serologically negatives, develops an arthritis, we are quite convinced of the non-luetic etiology of the joint condition. None of our patients had received any anti-luetic treatment previously. Recurrences, however, are not to be interpreted as evidence against the luetic etiology, any other manifestation of syphilis being liable to recur. It may indicate rather the need of a new course of treatment.

B. SYPHILITIC SYNOVITIS WITH JUXTA-ARTICULAR GUMMA.

CASE 8.—J. P., colored man, aged 40 years, is married, and his children are healthy. His wife had no miscarriages. He denies knowledge of venereal diseases. For 6 months he had had pain and had noticed a tumor at the outside of the left knee. He is in good physical condition and there are no signs or remnants of lues. At the lateral aspect of the knee joint there was a fibrous tumor about the size of a pigeon's egg. The joint was moderately distended by the fluid, and there was slight limitation of motion. At operation (by Dr. M. Galland) this tumor was found to be connected with the capsule of the joint. The joint cavity was opened during removal. The synovial tissue appeared to be inflamed and hypertrophic, with enlarged villi. About 10 cc. of a yellowish synovial fluid were obtained. The Wassermann reaction was 2+ in the blood and joint fluid. No synovial tissue was removed for examination. The tumor consisted of a yellow, fibrotic tissue. Microscopic slides showed a dense infiltration with round cells, especially perivascularly. There were some epithelioid cells and tuberculoma-like lesions with numerous giant cells. The histologic diagnosis by Dr. Henry L. Jaffé was gumma. After operation, a considerable effusion appeared and 20 cc. of a cloudy fluid were aspirated. The patient was given anti-luetic treatment and discharged. For other findings see Table 2.

The diagnosis in this case is chiefly based on the histologic findings of juxta-articular gumma. The weakly positive Wassermann in the joint fluid and the blood would have needed confirmation by repeated serologic examinations of the blood and joint fluid and a prolonged observation of the effect of both the specific and nonspecific treatment.

C. SYPHILITIC SYNOVITIS WITH OSTEOCHONDRITIS.

CASE 9.—I. D., a well-developed colored boy, aged 8 years, complained of pain in the left elbow and knee joint for 2 weeks previously. The elbow was normal; the knee was swollen and distended with fluid. Walking was possible without a limp and the pain on motion was only slight. There was no increase in general or local temperature. Sixty cubic centimeters of fluid were aspirated from the left knee. The Wassermann was 4+. Recumulation of fluid occurred in 12 days and 40 cc. of greenish, turbid fluid were aspirated. The Wassermann was 3+. For further findings see Table 2. The patient received only local applications of mercury and when he returned 1 month later both knee joints were swollen and fluctuating. The pain was only slight and the patient continued to walk. The blood Wassermann was 4+ and the Roentgen ray showed gouged-out areas at

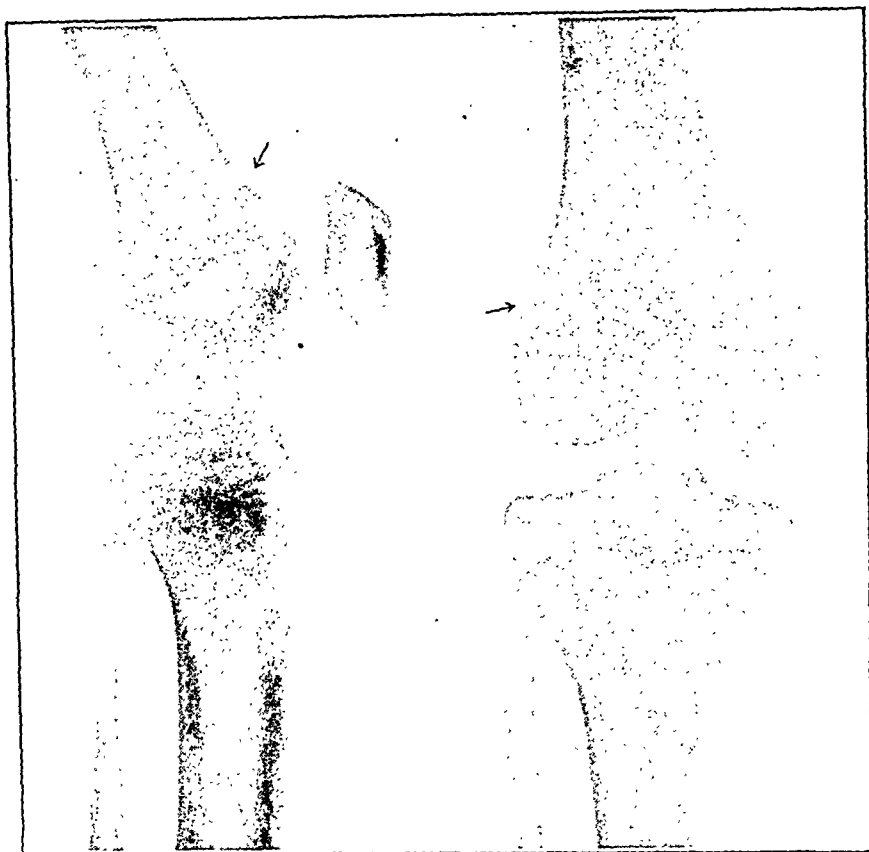


FIG. 1.—Case 8. Effusion in the right knee joint. Arrow indicates gouged-out area at osteochondral junction of the lateral condyle of the femur, and beginning periostitis.

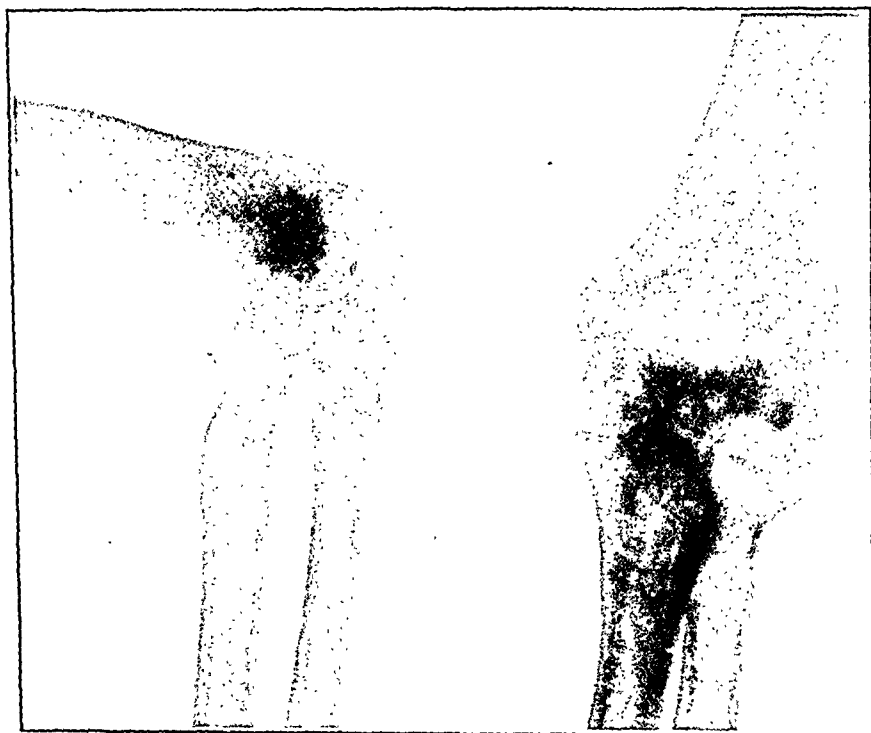


FIG. 2.—Case 10. Ankylosis of the left elbow. Rarefaction and sclerosis of the articular surface of the humerus (gumma) and periostitis.



FIG. 3.—Case 10. Effusion in the left knee joint. Gumma at patellar groove of the condyle of the femur (arrow to lateral view) and periostitis (arrow to antero-posterior view).

the osteochondral junction of both condyles of the femur and chondroperiostitis. The patient is now under general antiluetic treatment and the swelling has diminished.

In this case of congenital syphilis, the joint involvement consists of synovitis and early destructive and productive processes of the articular surfaces which are manifest in the Roentgen ray pictures. This strengthens the evidence of the syphilitic etiology; indeed, Dr. Pomerantz, director of Roentgen ray laboratory, made the diagnosis of congenital syphilitic arthritis from the Roentgen ray appearance alone.

D. SYPHILITIC SYNOVITIS OF THE LEFT KNEE JOINT AND GUMMA AT THE CONDYLE OF THE FEMUR. DESTRUCTION AND ANKYLOSIS OF THE RIGHT ELBOW.

CASE 10.—K. A., aged 27 years, in good general condition, denies syphilitic infection. He has had a bowing of the anterior aspect of the tibia since childhood. There has also been pain, swelling and stiffness of the right elbow, which progressed in spite of nonspecific treatment. On examination, the right elbow was found to be deformed and fixed in about 100 degrees of flexion. The Roentgen ray picture showed obliteration of the joint space and bony ankylosis, irregular rarefaction and sclerosis of the articular surfaces of the humerus, periostitis at the metaphysis, especially pronounced at the medial epicondyle of the humerus (Fig. 2). The left knee joint was swollen for 1 year. The patient walks with a limp and the knee joint was distended with fluid. Twenty cubic centimeters of greenish, turbid fluid were aspirated. The Wassermann test was 4+ in blood and joint fluid. For other findings see Table 2. The Roentgen ray showed periostitis of the metaphysis and epiphysis of the femur. An area of rarefaction and sclerosis is seen at the patellar groove of the femur and at the lateral condyle. The appearance is characteristic of gumma (Fig. 3). There is a small gouged-out area at the chondro-osteal junction of the medial condyle of the tibia. The patient received antiluetic treatment and the knee joint is greatly improved.

The negative history of infection and the malformation of the tibia indicate that this is a case of congenital syphilis. Two stages of a progressive, destructive syphilitic arthritis are presented. The pathologic process in the left knee joint shows chiefly synovitis and gumma at the articular surface of the femur. Although the Roentgen ray appearance is characteristic, involving chiefly only one epiphysis, the diagnosis of tuberculous arthritis was made by 2 radiologists. The older process at the elbow joint illustrates the disastrous effect of the diagnostic error. Here the process has led to destruction and ankylosis of the joint. The importance, therefore, of a careful analysis and complete examination of the joint fluids is emphasized.

TABETIC ARTHROPATHY. The joint fluid and the blood serum in 1 case gave a negative Wassermann reaction. In another case, not included in this series, both reactions were strongly positive. This fluid was hemorrhagic. These findings tend to confirm the view that the tabetic joint changes are produced by continuous injury and disorganization, due to loss of nerve function. Similar changes are found in traumatic and degenerative cord lesions (syringomyelia).

Tabetic arthropathy should therefore be eliminated as a form of syphilitic arthritis and included in the group of neuropathic arthropathies.

Summary. A well-defined group of syphilitic arthritis with effusions was isolated from the great variety of joint affections attributed to syphilis.

In a series of 112 cases of arthritis with effusion of various etiology and stage, this type of syphilitic arthritis is represented by 9 cases (8.1 per cent).

All occurred in the late stage of infection and at least 5 in congenital syphilis. None of the remaining 4 cases admitted infection; none had received antiluetic treatment.

The knee joint was involved in all cases; no other manifestations of lues were present in 8 cases.

The Wassermann reaction in the blood and joint fluid was strongly positive in 8 and weakly positive in 1 case.

The joint involvement was confined to an inflammatory process of the synovial membrane in 7 cases. One case was complicated by juxta-articular gumma; and another by osteochondritis and periostitis. Finally, 1 case which does not belong to this series presented a destructive form, leading to ankylosis of the left elbow and gummatous arthritis of the left knee joint.

Conclusions. The diagnosis has to establish first the presence of syphilis. In 7 cases this was based on the Wassermann reaction; in 2 cases other manifestations of lues were present (parenchymatous keratitis and juxta-articular gumma respectively).

More complicated is the second task, the proof of the syphilitic etiology of the joint affection. The complete examination of the joint fluid is necessary to rule out other conditions.

The positive Wassermann reaction in the joint fluid, in combination with negative other findings, is the most important evidence. The discrepancy between a history of trauma and the inflammatory character of a joint effusion in a syphilitic is suggestive.

Also the age incidence furnishes some clues, syphilitic arthritis being most frequent in children and young adults. The clinical picture of a monoarthritis or bilateral involvement of the knee joints with only slight degree of pain, muscle spasm, and peri-articular thickening without systemic manifestations, is further pertinent.

Roentgen ray evidence is available only when pathological changes have occurred at the articular surface, a condition which was present in 2 of our cases (20 per cent).

The therapeutic evidence is based on the inefficiency of non-specific and a characteristic response to specific therapy, consisting of no evident change or exacerbation of the type of the Herxheimer reaction after initial doses, and the final success of the full course of treatment, in the cases where destruction of the joint is not too far advanced.

Accurate diagnosis and successful treatment accomplish two results: first they restore the joint; and second they help to eradicate the syphilis.

NOTE.—The material for this paper was derived from the orthopedic services of Drs. Harry Finkelstein, Herman Frauenthal, Samuel Kleinberg and Leo Mayer, to whom I wish to express my gratitude.

Case 10 was a private patient of Dr. Harry Sonnenshein, to whom I am indebted for the use of the case for publication.

I wish also to thank Dr. Maurice Pomerantz, director of the Roentgen ray Laboratory of the Hospital for Joint Diseases, for his coöperation in the study of the Roentgen ray plates.

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ASEPTIC PURULENT MENINGITIS.

REPORT OF SIX BENIGN CASES.

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THE complication of a purulent meningitis secondary to neighborhood suppurative foci in the head or systemic infection is almost always considered to be a grave malignant condition. The occurrence of a series of 6 rather unusual cases of secondary purulent meningitides of benign character with recoveries in all has prompted this investigation of the subject.

There is an extreme paucity of literature upon the subject and we had difficulty in finding cases similar to ours, but we believe there must be a larger number of these cases than the literature would indicate.

In reviewing the literature of benign cases of meningitis other than the epidemic type, we investigated the following author's studies: Mygind¹ reported a series of 210 cases of otogenic meningitis and found 59 cases (28 per cent) recovered. The greatest number of these benign types of meningitis were secondary to lateral sinus thrombophlebitis. Only 10 per cent of the cases that recovered contained bacteria. Those that contained bacteria and recovered were usually streptococcic. Other pyogenic bacteria were more malignant. There are a few other isolated case reports of secondary streptococcic meningitis with recovery although it is common knowledge that streptococcic meningitis has a mortality of about 90 per cent. In the case reports of recoveries there has usually been a removal of the primary focus of infection, *i.e.*, mastoidectomy or lateral sinus drainage with jugular ligation, etc. Huenchens² reports such a case. Walthall³ reported a case of meningitis, similar to ours, secondary to mastoiditis and extra dural abscess that showed a sterile purulent spinal fluid and recovered. Estiu and Lenci⁴ report a case of aseptic purulent meningitis of unknown etiology with recovery.

Viets and Watts⁵ reported 5 cases of aseptic lymphocytic meningitis, all of which had low spinal fluid cell counts and a symptom complex similar to encephalitis or a meningitic type of poliomyelitis. This in our opinion is an entirely different type of meningitis from

our cases and it is difficult to prove this type as a meningitic clinical entity. Guenther⁶ from the Gothenburg pediatric clinic in an extensive article upon this type of meningitis, reported 13 cases of meningitis also showing a lymphocytic reaction in the spinal fluid. In his review of the literature he found about 100 similar cases over a 20-year period. He concluded that these are acute aseptic meningitides of unclear etiology and attempted to establish a nosologic entity. However, he admits they resemble meningitic poliomyelitis or encephalitis. Tuberculosis was excluded because the cases tend to recover.

Quinke,⁷ the originator of spinal puncture, established a clinical entity called meningitis serosa. This is an aseptic type secondary to neighborhood or systemic infection, but shows little if any cellular reaction in the spinal fluid. Apparently this type is a toxic meningitis or so-called meningismus.

Baudouin⁸ reported an interesting case of aseptic purulent meningitis following cerebral concussion without skull fracture. The case recovered promptly and the author concluded the case was the result of cerebral irritation secondary to the contusion. This case may have been simply meningeal reaction secondary to absorption of small hemorrhage.

Capecci⁹ reported a case of traumatic meningeal apoplexy, complicated by two attacks of aseptic purulent meningitis at monthly intervals, that recovered. He concluded the meningitis was secondary to a circumscribed infection in the neighborhood of the meninges from the skull fracture. This case is similar to Case 4 in our series.

Although the etiology of the purulent meningitis cannot be proved in all our cases, the clinical evidence is strong that in 4 cases the meningitis was secondary to ruptured brain abscesses and in 2 from ruptured cysts. In all cases the spinal fluid was cloudy (purulent) containing a high percentage of polymorphonuclear cells and all were sterile upon culture. One case was apparently of traumatic origin. Spinal drainage was used in all cases except 1 that required the relief of subarachnoidal blockage first by a cerebellar decompression and later by ventricular drainage. The most valuable prognostic criterion has been the sterility of the spinal fluid; namely, absence of bacteria either in smear or culture.

Case Reports. CASE 1.—Ruptured subdural abscess with secondary aseptic purulent meningitis, from sinus disease.

T. A., aged 35 years, married, had an exenteration of the ethmoid sinuses on May 17, 1929, on account of intermittent pain over the eyebrows and was dismissed from the hospital in good condition. On the way home from the hospital (May 20) a sudden upper cervical pain, throbbing and shooting in character, from the occiput to the shoulders developed. The pain increased in severity and was made worse upon head movement and coughing. It was accompanied by vomiting at times. The patient returned to the hospital.

Examination on May 21, 1929, revealed a very sick man, temperature 101° F., with a rigid neck that produced marked pain upon attempted

flexion of the head. All deep reflexes were exaggerated, tremor was present in the hands. Bilateral Kernig's signs were present but focal paralytic signs were absent. The spinal fluid was markedly increased in pressure, containing 1000 cells, with 90 per cent polymorphonuclears per cubic millimeter. Thirty cubic centimeters of fluid was removed and antimeningococcic serum given intracisternally. The smears of the fluid revealed no bacteria, but marked cellular degeneration was present. Repeated cultures on brain broth and blood agar were sterile.

Progress: On the 22d the patient was lethargic, a slow pulse and a partial right third nerve palsy appeared. The blood showed a leukocytosis of 25,300, of which 90 per cent were polymorphonuclear cells. Daily spinal or cisternal drainages were done. By the 25th the pressure was normal and the cell count 230 per c.mm.; on the 21st, 1000 cells and 3000 cells; 22d, 7000 cells; 24th, 900 and the 25th, 230. On the 23d, on account of the right third nerve palsy, a frontal trephine was made on the right side through the frontal sinus. This region was explored subdurally back to the sphenoid region without locating a source of pus. A puncture of the anterior horn of the ventricle revealed clear fluid. The patient left the hospital in 2 weeks, symptom free and has continued in excellent health.

Roentgen rays of the ethmoids showed them poorly visible, the right sphenoid was either not developed or diffusely cloudy.

Comment. This case represents an aseptic purulent meningitis secondary to ethmoid and sphenoid sinusitis and was probably the result of a ruptured sterile subdural abscess. The clinical picture was that of a malignant meningitis at first but repeated spinal fluid studies, with the degenerated type of cells and the absence of bacteria soon revealed the benign character of the pathology.

CASE 2.—Ruptured subdural abscess with secondary aseptic purulent meningitis from sinus disease.

Mr. E. R., aged 28 years, single, was admitted to the hospital September 18, 1929. The following history was obtained from the parents. For the past year the patient had suffered from a dull frontal headache, diagnosed as chronic sinusitis. Five intranasal operations had been performed. About 10 days previously the headaches became more severe. On September 16, the headache suddenly became worse, the patient vomited and became delirious. At this time the family physician found a suggestive Kernig reflex, leukocytosis of 24,000 and sent him to the hospital with a diagnosis of brain abscess. During the automobile trip of 300 miles the patient was irrational and violent, and was admitted under the influence of narcotics.

Examination: The patient was very restless and delirious, both optic disks were slightly blurred, marked neck rigidity and bilateral Kernig were present. The reflexes were all hyperactive, no focal paralyses were present. A spinal puncture showed pressure of 30 mm. of mercury. The fluid was purulent containing 3000 cells, 90 per cent of which were polymorphonuclear cells, but no organisms were found in the smear. The protein content was 45 mg. per 100 cc. The fever ranged from 100° to 102° for 17 days; pulse, 64 to 100; the blood leukocytes, 18,700, of which 88 per cent were polymorphonuclears.

Head Roentgen ray study demonstrated the frontal sinuses as pneumatic. The right ethmoids showed some haziness in outline. The posterior ethmoids appeared to be broken down and the area represented by thickened membrane. The posterior sphenoids on the left were well visualized. It was the opinion of the roentgenologist that the ethmoids had been the seat

of previous infection, the brunt of which had been carried by the left middle ethmoids.

Progress: On the 19th the severe headache continued, the patient was in stupor, involuntary muscular twitchings were present, but no focal neurologic signs were present. The spinal fluid under 14 mg. of mercury pressure was less turbid, the cell count was 1000 per c.mm. The cultures of the fluid were all sterile. Spinal drainage was continued daily with a gradual clearing up of purulency; after about 4 weeks the patient was discharged from the hospital, continuing to feel somewhat weak and suffering from headache which gradually lessened in severity. At the present time the patient is symptom free, working and apparently in normal health.

Comment. This case was very similar to Case 1, namely, secondary purulent meningitis from ethmoid sinusitis with a probable intermediary stage of subdural abscess with final rupture producing a sterile meningitis. Again repeated spinal fluid studies revealed the benign character of the disease which at first seemed malignant.

CASE 3.—Staphylococcic bacteremia, multiple body abscesses, sinusitis, osteomyelitis of frontal bone, left frontal lobe abscess with recurrent attacks of purulent aseptic meningitis.

Mrs. G. T. D., aged 25 years, was first admitted to the University Hospital on August 7, 1925, with symptoms and findings of acute left frontal and ethmoid sinusitis. The examination was negative except for a markedly swollen left eye, bilateral optic neuritis, fever and leukocytosis. Head Roentgen ray showed extensive left frontal osteomyelitis. On August 8 and 15, sinus operations were performed on the frontals and ethmoids. On August 21 a breast abscess was drained and on the 26th an abscess was opened in the region of the right hip. At this time the patient was very toxic and at times was irrational. The blood culture was positive for staphylococcus aureus. In November intracranial pressure symptoms appeared in the form of stupor, increasing headache, and vomiting. Right-sided pyramidal tract signs were present. On November 25 a trephine was made by Dr. J. J. Keegan, through the left frontal sinus region and a brain abscess was drained from the left frontal lobe. About 1 ounce of pus was removed from which a pure culture of staphylococcus was cultured. The patient continued to run a stormy course; from the onset fever was constantly present as high as 105° F. for 60 days. On January 7, 1926, there was considerable cortical herniation with sloughing tissue. On January 28, 1926, this herniation was cut away and a large sequestrum was removed from the orbital plate. Blood cultures were positive for staphylococci on 2 occasions, the leukocytes were usually high from 24 to 30,000. On February 11, 1926, the patient was dismissed from the hospital in fair condition.

The patient was readmitted on June 26, 1928, on account of recurrent cerebral symptoms in the form of right-sided convulsive seizures, attacks of aphasia, stupor and fever, with temperature of 105° F. Signs of meningitis were present. Daily spinal punctures were performed. The fluid was cloudy and under markedly increased pressure with cell counts ranging from 200 to 3000, of which 90 per cent were polymorphonuclear cells. All specimens were sterile to culture upon a number of different media. The left frontal region was again explored and more pus was drained. The patient left the hospital in fair condition in about 3 weeks' time.

On October 15, 1928, the patient was again readmitted in a critical condition on account of the same symptoms present in June. At this time the spinal fluid was again 20 to 22 mm. of mercury pressure, turbid with polymorphonuclear cells from 500 to 1000 per c.mm. All cultures of the spinal

fluid were again sterile. Double choked disks of 4 diopters were present. On November 20, the patient was again explored in extremely critical condition and about 1 ounce of creamy pus drained from the frontal lobe. A stormy convalescence followed with recurrent attacks of meningitis. On December 4, when the spinal fluid contained 4000 cells per c.mm. only about 5 cc. of fluid could be drained, the condition suggesting a block of the foramen magnum. The spinal fluid cultures were still sterile, but each culture from the brain abscess contained staphylococci and at one time some streptococci. The fever was high, up to 104° F. for 35 days. On the 88th day the patient was again dismissed in fair condition.

The patient returned again for a few days' observation in 1929 on account of a psychoneurotic upset. In 1930 she went through a normal pregnancy and has shown no other evidence of return of the infection. The patient was reexamined in March, 1931, on account of occasional convulsive seizures. An encephalogram showed moderate hydrocephalus and extensive arachnoiditis, especially over the left frontal lobe. She probably will continue to suffer from symptomatic epilepsy.

Comment. This patient represents an interesting type of recurrent sterile purulent meningitis secondary to chronic brain abscess. The etiology was sinusitis complicated by osteomyelitis and a staphylococcemia. It seems an accident that this patient recovered, as the disease was always of malignant character. By the time the cerebral complications occurred the patient's immunity was high or the organisms reduced in virulence. It is interesting that organisms were easily cultured from the brain abscess but could never be demonstrated in the spinal fluid.

CASE 4.—Head trauma followed by two attacks of cerebrospinal fluid block, ruptured brain abscess with purulent aseptic meningitis.

Mr. H. A., aged 20 years, when first examined on April 26, 1925, gave the following history: On February 16, 1924, the patient slipped and fell upon icy ground striking the occiput on a tree. He got on his feet immediately, walked 3 blocks then fell unconscious. He remained unconscious for 4 hours. Upon coming to, the patient suffered severe pain in the occiput and back of neck and felt nauseated. After 1 week's osteopathic treatment the patient felt well and returned to work.

Several days later upon stooping he noticed a headache, which continued with exacerbations upon effort or hard work. In March and April, 1925, the headaches became more intense and at times were accompanied by vomiting.

At the examination on April 26, the patient was groaning with pain, pulse rate 46. The facies were flushed, retracted rigid neck and double choked disks were present. An acute cerebrospinal fluid block was obviously present. The patient was taken to the hospital immediately. Dr. J. J. Keegan performed a suboccipital decompression. The dura was very distended and the arachnoid appeared thickened. A tentative diagnosis of arachnoiditis was made. Later events indicate that the condition was entirely a pressure phenomenon.

Following the operation the acute pressure symptoms subsided, the neck rigidity remained for several weeks before subsiding.

Reexamination on May 23, 1925, showed no objective neurologic findings, although the patient still complained of some headache and dizziness. On August 23, 1925, the neurologic examination was negative; the patient was doing light work and felt well.

On December 5, 1925, the spinal fluid was under 16 mm. of mercury pressure. The cell count, protein content, Wassermann and Lange tests were negative. The patient complained of dizzy spells. Outside of the increased spinal pressure reading the examination was again negative.

In February, 1926, another examination was normal, the spinal pressure was 12 mm. of mercury. On August 23 the patient was hospitalized again for spinal puncture. The physical and neurologic examinations were normal. The spinal pressure was 10 mm. of mercury. A few hours following the puncture, the patient complained of sudden severe head pain, and vomited. The temperature was 101° F., pulse 55 to 65, the head was retracted, neck rigidity and bilateral Kernig were present. The findings were those of an acute cerebrospinal fluid blockage. Dehydration treatment was ineffectual. A ventricular puncture was done and 45 cc. of purulent spinal fluid was removed which contained 3200 pus cells per cubic millimeter. No organisms were found on smear and the fluid was sterile to culture. Following the ventricular drainage the patient's condition improved, the fever gradually subsided and the leukocyte count of 22,000 became normal. The patient was dismissed in fair health on August 31, 1926. The diagnosis was ruptured sterile brain abscess with secondary aseptic purulent meningitis.

The patient has been reëxamined at frequent intervals since that time but he has not shown any symptoms of recurrent trouble. At present he is working and apparently in normal health.

Comment. In this case the primary etiology is difficult to explain. The entire symptom complex apparently began with the head trauma. The most logical explanation for the purulent meningitis was a ruptured sterile cerebral abscess. The nature of the abscess formation is difficult of explanation. The abscess ruptured into the ventricles rather than into the subarachnoid space. The abscess produced 2 attacks of foramen magnum blockage which required first a cerebellar decompression and later a ventricular drainage for relief. The final rupture of the abscess was possibly produced by a spinal puncture. The meningitis, although purulent was again of aseptic character as shown by absence of bacteria.

We have recently observed another interesting case of cerebral abscess that followed a stab wound in the frontal bone about 14 years ago. The abscess ruptured while the patient was under observation in the hospital. The resultant meningitis was not entirely aseptic as organisms were cultured upon one occasion, after 72 hours' incubation. In spite of the relatively benign character of the meningitis the patient died. The necropsy revealed the traumatic abscess entirely evacuated. There still remained some fibrinopurulent exudate in the subarachnoid cisterns. There was no cerebral edema and the brain sections were normal. The cause of death was obscure. We have not included this patient in our series because the meningitis was not entirely aseptic. The clinical picture was similar to Cases 1 and 2 and the meningitis was of benign type. The bacteria found were not of virulent type and could only be demonstrated with great difficulty.

probably sterile at the time of rupture. All cases recovered and all the spinal fluid cultures were sterile. In 2 cases the apparent etiology of the presumed subdural abscess was chronic sinusitis. In 1 other case the abscess (intracerebral) was secondary to frontal sinusitis that had also produced a metastatic pyemia. In 1 case the etiology was not clear, but it was presumed that an intracranial abscess developed posttraumatic, finally rupturing into the ventricles. In 2 cases puriform meningitis followed ruptured cysts, 1 a brain cyst and another a ruptured meningocele.

The most valuable diagnostic guide was the spinal fluid studies. In some cases, cellular degeneration, debris and atypical cells were present that suggested a lining membrane from abscess or cyst. This observation gave a clue that the meningitis was secondary to ruptured tumor. In all cases the absence of bacteria upon repeated smear and culture studies indicated a benign or sterile type of inflammation.

Spinal drainage was the most important single therapeutic procedure. In 1 case pressure complications required decompression and ventricular drainage.

We believe that this type of benign meningitis is more common than the literature review would indicate and may account for some reported recoveries of types that were presumed to be of malignant character.

In our opinion the etiologic factor of secondary meningitis from ruptured brain abscess should be more frequently considered in a differential diagnosis of atypical meningitides. Vigorous spinal drainage should be instituted in cases of secondary meningitis in the hope that the infection is benign.

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SPASMODIC TORTICOLLIS: RESULTS OF REMOVAL OF FOCI OF INFECTION AND TREATMENT WITH SPECIFIC VACCINE.*

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BETWEEN January 1, 1910, and January 1, 1929, 534 patients suffering from all types of torticollis were admitted to The Mayo Clinic. For this study patients who had suffered from the spasmodic type of torticollis and who had received medical treatment were considered. Patients suffering from other types of torticollis and all of those who had undergone orthopedic or neurologic surgical procedures were not included in this study. Thus, there were left for our study 247 patients to whom letters of inquiry were addressed and from whom we obtained 100 replies. These were carefully studied, and 18 were excluded because of insufficient data, the death of the patient (in no instance attributable to torticollis) or because the patient presented associated neurologic disturbances.

Of the 82 patients who remained 39 were women and 43 were men. The average age of the patients at onset of the condition was 39 years; their average age at the time of admission to the clinic was 44 years; the average duration of symptoms prior to their admission to the clinic was 5 years. The average duration of symptoms of patients who continued to suffer from torticollis at the time of this inquiry was 12 years. Those patients who reported complete disappearance of all symptoms had had their symptoms for an average of only $3\frac{1}{2}$ years.

At the time of the inquiry 44 patients (54 per cent) had not improved, 16 patients (19 per cent) were entirely relieved of the torticollis and 22 patients (27 per cent) reported improvement. It is difficult to evaluate the group listed as having "improved" for this is purely the patient's personal opinion. We have, therefore made no effort to separate this group into degrees of improvement. In some aspects of the study we were interested in knowing in how many cases the torticollis was stationary, and in how many there was improvement, either partial or complete. In such instances the cases in which the condition had improved and in which it had disappeared were listed together.

Removal of foci long has been advocated as an essential part of treatment. In determining the results which followed removal of foci of infection it is necessary to know whether the patient for

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whom removal of foci was advised had followed the advice. Fifty-four of 58 patients who had been advised to have teeth removed followed the advice; 4 did not. Five of the 21 patients who were advised not to have teeth extracted followed the advice; the other 16 of these 21 did not state whether they had had teeth extracted. In 3 cases it was not stated what the advice had been concerning extraction of teeth, nor did the patients state what course they had followed in this respect. Thirty-seven of the 42 patients for whom tonsillectomy was advised underwent the operation; 5 did not. Of the 33 patients for whom tonsillectomy was not advised 1 had the tonsils removed, 17 of the 33 did not (in 11 of these 17 cases tonsillectomy had been done before the patients were admitted at the clinic), and 15 of the 33 did not state whether or not they had had their tonsils removed. In 7 cases it was not stated whether or not the patients had been advised to undergo tonsillectomy and the patients did not state whether or not they had undergone the operation.

In Table 1 is a comparison of the number of patients for whom tonsillectomy and removal of teeth, either or both, was advised. Thirty-five patients gave evidence of focal infection in both teeth and tonsils. In only 1 instance was focal infection elsewhere in the body found and treated; this patient had a nonspecific infection of the prostate gland.

TABLE 1.—CASES IN WHICH REMOVAL OF TEETH AND TONSILS, EITHER OR BOTH, WAS ADVISED.

	Infected teeth.			Total
	Extraction advised.	Extraction not advised.	Not stated	
Infected tonsils:				
Removal advised	35	7	..	42
Removal not advised	23	10	..	33
Not stated	4	3	7
Total	58	21	3	82

In Table 2 the cases are listed as to whether foci of infection were removed. The table notes, furthermore, whether, on the one hand, torticollis had remained stationary, or, on the other, whether it had disappeared or improved. There was a difference of 15 per cent in the improvement or disappearance of the torticollis in favor of removal of foci. There are, of course, factors which might affect the validity of this difference of 15 per cent. The largest factor is the possibility that this may be merely a sampling difference; in other words, that a similar group of 82 patients might not reveal this difference. Using the Chi square theory of determining the probable significance of the difference between proportions, it is found that there are 79 in 100 chances that this is a difference greater than would arise from sampling. In order to have a 96 per cent chance of this difference of 15 per cent being absolutely valid, it

would be necessary to have a series of 221 cases. Although we are unable to determine with absolutely certainty that this is a significant difference, yet we have reasonable grounds for the assertion that the difference between 51 per cent improvement or cure after removal of foci and 36 per cent without removal of foci is of sufficient significance to warrant continuance of this procedure.

TABLE 2.—IMPROVEMENT AND LACK OF IT IN RELATION TO REMOVAL OF FOCI AND CONTINUED PRESENCE OF FOCI.

	Condition of torticollis.		Total.	Per cent of patients improved or cured.
	Stationary.	Improved or disappeared.		
Foci of infection removed	28	29	57	51
Foci of infection not found or not removed	16	9	25	36
Total	44	38	82	46

The other form of treatment most commonly advised was the use of specific vaccines.

TABLE 3.—IMPROVEMENT AND LACK OF IT IN RELATION TO ADEQUATE, INADEQUATE AND NO TREATMENT BY SPECIFIC VACCINE.

	Condition of torticollis.		Total.	Improved or disappeared (per cent).
	Unimproved.	Improved or disappeared.		
Adequate specific vaccine therapy	9	6	15	50.0
Inadequate or no specific vaccine therapy	35	32	67	47.8
Total	44	48	82	46.0

In Table 3 we have listed all cases in which vaccine was given and the condition of the torticollis. We have arbitrarily defined as a satisfactory trial of vaccine the administration of vaccine for a period of at least 3 months. In every instance this vaccine was prepared at The Mayo Clinic. It is found that in 40 per cent of this group of cases the torticollis improved or disappeared, as compared to 47.8 per cent in cases in which no specific vaccine treatment was given or the period of treatment was inadequate. According to the Chi square theory of determining the probable significance of the difference between proportions, there are 58 in 100 chances that this is a difference which might arise as a sampling process. That is, these percentages might be reversed were 82 other patients with torticollis similarly studied. Therefore, conclusions cannot be drawn from this difference of 7.8 per cent. As Rosenow has said: "The benefits which follow the removal of foci proved to contain organisms and the use of autogenous vaccine, although often striking, do not occur regularly enough to prove etiologic relationship."

Table 4 is included only because it is of interest to know to what cause the patients attribute their disability. It is self-explanatory,

and because it is based entirely on the patient's ideas and not on any scientific study or clinical impression, conclusions are not drawn from it.

TABLE 4.—PATIENT'S OPINION AS TO CAUSE OF TORTICOLLIS.

Patient's opinion of cause.	Condition of torticollis.			Total.
	Stationary.	Disappeared.	Improved.	
Nervousness, worry, overwork, etc.	10	7	5	22
Focal infection, exposure, etc.	6	7	4	17
Trauma	7	..	7	14
Not stated	21	2	6	29
Total	44	16	22	82

It is also of interest to know to what procedure the patients attribute their improvement. Twenty-eight of the 38 patients in whom the torticollis disappeared or improved answered this question. Twelve gave credit to rest and relaxation, 5 to removal of foci, 2 to osteopathy, 2 to patent medicine and 1 each to vaccine, vaccine and rest, thyroidectomy, medicine, Christian Science, removal of foci together with chiropractic and chiropractic alone. The character of this information again precluded the possibility of drawing any conclusions from it.

Summary. A study has been made of 82 patients who had received medical treatment for spasmodic torticollis. Thirty-nine of the patients were women and 43 were men. The average age at onset was 39 years, the average age at admission to the clinic was 44 years and the average duration of symptoms prior to admission to the clinic was 5 years. The average duration of symptoms of those patients who continued to suffer with torticollis to the time of this inquiry was 12 years. Those patients who reported complete disappearance of all symptoms had had symptoms for an average of only $3\frac{1}{2}$ years. Forty-four of the 82 patients (54 per cent) were not improved; 16 patients (19 per cent) reported complete disappearance of symptoms; 20 patients (27 per cent) reported improvement. The patients coöperated well when advised to have foci of infection removed. Fifty-one per cent of the patients who had foci of infection removed reported improvement or disappearance of the torticollis, as compared to 36 per cent of those who did not have foci removed. This difference of 15 per cent is considered to be of sufficient significance to support the belief that removal of foci is warranted.

Conclusions cannot be drawn from this series as to the value of specific vaccine treatment for spasmodic torticollis.

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THE CLINICAL CYCLE OF GOITERS.

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CLINICIANS and pathologists are still describing their findings in the stages of goiter transformation as representing certain distinct types of goiter. Attempts have been made during the last three generations to make the clinical and histopathologic pictures of goiters coincide; but as much confusion still exists as originally, and it would seem that the problem should be approached from a different angle.

The more one studies patients suffering from thyroid enlargements, and tries to correlate the clinical and pathologic findings, the more he finds that there are many discrepancies between the two, and to consider the types as clinical entities is frequently misleading. There have been a few observers during recent years who have maintained that the types of goiter as merely representing stages of a continuous disease process. Hertzler³ was one of the first to teach this, as he had observed the life cycle of his patients, and had not confined his observations to the signs and symptoms at a given period of the disease. In previous publications^{4,5} I have reported cases to prove that these different types do not represent clinical entities. Boyd,¹ in his recent addition on surgical pathology, states: "Goiters are usually divided into three main groups, which are regarded as being entirely distinct entities. The first is known as simple or endemic (colloid) goiter, the second as adenomatous, the third as exophthalmic goiter. With the exception of the second, these names are purely clinical and have no pathological connotation. The second is certainly pathological, but it is unjustified for the nodules are not adenomata in the pathological sense."

Keilty,⁷ in an article based on the pathologic study of 1000 thyroid glands, states: "Following the combined study of histories, gross specimens and microscopic slides over a period of 10 years, the opinion is expressed that a large proportion of nodular thyroid glands, toxic and nontoxic, show the pathological evidence of chronic productive, and contractive thyroiditis rather than of adenoma."

The following cases will serve to illustrate the confusion that still exists if one tries to pigeon-hole the diagnosis from the findings at certain stages of the disease.

Case Reports. CASE 1.—A female, aged 17 years, was admitted to the thyroid clinic on July 17, 1930, complaining of enlargement of her neck.

Patient first noticed enlargement of the neck at the age of 9 years, at which time she was treated by her family physician for 1 year and later in this institution for several months with iodine and thyroid medication, but noticed no improvement and discontinued treatment. For the past 4 years her neck was gradually enlarged, but she has no other complaints. Examination revealed nodular enlargement of the thyroid in both right and left lobes, the neck measuring 33 cm. and basal metabolism -8 on July 14, with all other laboratory work negative. Diagnosis of bosselated goiter was made, following Hertzler's teaching, or if one uses the accepted classification, a diffuse adenomatous goiter. Patient was put on thyroxine, $\frac{1}{80}$ gr., intravenously, every 2 weeks, and thyroid extract, 2 gr. t. i. d. by mouth. She has shown marked improvement under medical treatment, and at this time the enlargement has diminished 75 per cent. This case represents a type of goiter that is frequently operated upon, while in reality the nodules were produced by the connective tissue formation in the gland.

CASE 2.—A female, aged 17 years, was transferred to our clinic December 18, 1930, having been treated in another clinic in the hospital for 7 years. She complained of enlargement of her neck, which was getting worse. Patient had been treated at the Post-graduate Hospital for 7 years, taking iodine and thyroid extract. At the time of her admission a diagnosis of adolescent goiter was made, and although she has been under continuous treatment a lump was noticed in the region of the isthmus about 2 years previously, which has gradually enlarged. Basal metabolism was -6 on December 16, 1930. Patient has been on iodine and thyroid medication since entering our clinic without any improvement; diagnosis of adenoma of the isthmus being made which will necessitate an operation. This patient, although under continuous observation for 7 years, developed an adenoma while being successfully treated for an adolescent goiter.

CASE 3.—Female, aged 39 years, was admitted to the thyroid clinic February 5, 1931, complaining of nervousness and loss of weight for 2 to 3 months. Past history negative. Patient has been well until 2 or 3 months before admission when she gradually began to decline and has been losing weight, estimated at about 20 pounds. She has become extremely nervous and has palpitation of the heart, also enlargement of her neck and prominent eyes. Examination revealed exophthalmos, enlargement of the thyroid with a thrill over the gland and pulse 140, her basal metabolism rate being $+64$ on February 15, 1931. Patient was advised admission to the hospital and was put on iodine and sedatives for 3 weeks before being operated upon. A one-stage thyroidectomy was done on March 4, 1931. Pathologic findings revealed Basedow's disease with included fetal adenoma. Although this patient gave a relatively short history, the pathologic study revealed an exophthalmic goiter with an adenoma which could not be detected on physical examination.

CASE 4.—A female, aged 64 years, was admitted to the thyroid clinic September 11, 1930, complaining of enlargement of her neck and difficulty in swallowing for the past few years. Patient states she had the enlargement of her neck since a young girl, at approximately the age of 16 years, and this has gradually become larger and about 10 or 15 years ago she noticed irregular nodules in her neck which have enlarged gradually and at the present time she has difficulty in swallowing and breathing. Examination reveals definite nodular masses in both lobes of thyroid. Roentgen rays of the chest on September 26, 1930, revealed a deviation of trachea and esophagus to the left with calcification of the lower poles of the thyroid. Basal metabolism was -1 on September 25, 1930. A diagnosis of calcified adenomata of the thyroid was made. The patient was operated upon on October 10, 1930, and the pathologic report revealed an adenocarcinoma of the thyroid with extensive calcification.

These cases represent what is routinely found in any clinic dealing with thyroid diseases if careful histories are taken, and the clinical and pathologic findings are correlated. Other cases could be cited to illustrate that the apparent types of goiters are interchangeable, if one follows the patient for a sufficient length of time or gets an accurate history.

Comment. It is difficult for one to believe that the thyroid gland could develop in itself colloid, adenomatous and exophthalmic goiters which are clinically and pathologically distinct entities; also chronic thyroiditis, Riedel's struma and Hashimoto's disease, which represent different pathologic entities. In clearing up any misunderstanding that exists in the pathologic study of this disease, it is essential to have a clear conception of the normal histology for the different periods of life, from stillbirth to senility. In a study⁶ of people meeting with accidental death from stillbirth to over 80 years of age, it was found that the normal histologic picture varied greatly for people of relatively the same age, and it is difficult to draw conclusions as to what constitutes normal thyroid histology. This being so, it is even more difficult to classify the abnormal.

When we come to consider thyroid diseases we have to admit a dysfunction of the gland, which is first manifested by colloid deposits during adolescence or in later life. Sometimes this stage of the disease responds to medical treatment, while on the other hand the enlargement may spontaneously disappear. If there is an accompanying chronic thyroiditis for a number of years, which may vary greatly in severity, the connective tissue which is produced by this process will ultimately produce nodules, or so-called adenomatous goiter, while on the other hand the patient may develop an exophthalmic goiter before the nodular stage is reached. It is difficult, and sometimes impossible, to palpate a thyroid enlargement in a typical exophthalmic goiter, so how can we say that there has not been a colloid disturbance preceding the exophthalmic goiter which was never detected by the patient, or by the family physician?

In considering chronic thyroiditis, Riedel's struma and Hashimoto's disease, one is confronted with trying to place these types of disease in the cycle of pathologic changes. Graham and McCullagh,² after a most thorough study of 4 cases of Hashimoto's disease, state: "An acceptable explanation of the pathogenesis of the changes in the thyroid is not apparent. It would be simple enough to follow the line of least resistance and agree with one of the prevailing views, *viz.*, that struma lymphomatosa is the early stage of Riedel's struma. A review of the literature and personal experience with both types of lesions have inclined us to the view that they are quite dissimilar. Riedel's struma more nearly approaches a true inflammation than does the lesion described by Hashimoto's." As the other types of goiter are now being con-

sidered as stages of a continuous disease, it may be that ultimately chronic thyroiditis, Riedel's struma and Hashimoto's disease will be proved to be of an inflammatory nature and the difference in the findings will be due to the response to the infection.

Conclusion. From a clinical point of view it would be much simpler for us to regard the different goiters as stages of a continuous disease process and treat all cases medically unless hyperthyroidism, pressure symptoms or an encapsulated tumor actually exists. In this way some of the nodular goiters that are called adenomata would be found to be colloid rests from connective tissue formation, and these will in turn respond to iodine or thyroid medication, thus saving many needless operations.

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REVIEWS.

ELECTROTHERAPY AND LIGHT THERAPY. By RICHARD KOVÁCS, M.D., Clinical Professor and Director of Physical Therapy, Polyclinic Medical School and Hospital, New York. Pp. 528; 211 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$6.50.

THE preface states that this volume had its conception in the conviction that practising physicians should be shown the possibilities and limitations of that part of modern physical therapy which they themselves can carry out in their own offices. There is no doubt that physical therapy has been largely accepted as an integral part of the practice of medicine and surgery. This book should prove useful not only to the physician who actually practices electrotherapy and light therapy as a specialty, but it should be equally valuable to the practitioner who wishes to gain information as to what is being done in this field of treatment. The Reviewer would particularly invite attention to the several brief but excellent chapters on Electrophysics and on Photophysics. B. L.

A TEXTBOOK OF NEUROANATOMY. By ALBERT KUNTZ, PH.D., M.D., Professor of Microanatomy in St. Louis University School of Medicine. Pp. 359; 197 illustrations. Philadelphia, Lea & Febiger, 1931. Price, \$5.50.

THIS book has been written to aid the student in his first attempts to gain some knowledge of the anatomy and physiology of the nervous system. The author bases his presentation on the assumption that the fundamental plan of structure is relatively simple, though the anatomical structure is somewhat intricate. The subject is considered in twenty-two chapters, of which four, comprising nearly one-quarter of the book, are devoted to the cerebral hemispheres. The illustrations of actual tissues are derived from a variety of sources, and there are many diagrams of the courses of tracts. At the ends of the chapters are lists of references to the literature which will be useful to the student seeking further information. W. A.

THE TREATMENT OF ASTHMA. By A. H. DOUTHWAITE, M.D., F.R.C.P. (LOND.), Assistant Physician, Guy's Hospital. Pp. 164. New York: William Wood & Co., 1931. Price, \$2.50.

THE asthma problem is presented from a European viewpoint, as yet not deeply influenced by the work of numerous American investigators in this field, especially from the standpoint of hypersensitiveness. Of 46 references in the book there are only 4 to the extensive American literature. While the many therapeutic measures which have been employed in the treatment of this disease receive the author's attention, there are numerous statements which must be challenged: "It is, of course, impossible to test out all the possible allergens separately." In suggesting tests with groups of related allergens, he says: "One group may consist of dust, fur, feathers and orris-root extracts." The statement that "In the case of children it is seldom practicable to perform skin tests because of the fear induced by scalpel or hypodermic needles" is certainly not in keeping with the experience of American allergists. Nor is his quotation of Moos that "Skin reactions to proven allergens fail to appear after adequate psychotherapy." Nor this: "Permanent residence at high altitudes can be relied upon to abolish the paroxysms in nearly every case." While he recommends the treatment of pollen-sensitive patients with pollen extracts, he deplors the length of time and expense involved: a proper objection to his own method in which he gives prophylactic injections every other day beginning early in December. The practitioner will find sounder advice in any one of a number of current American texts.

R. K.

THE INBORN FACTORS IN DISEASE. By A. E. GARROD, K.S.M.G., D.M., LL.D., F.R.C.P., F.R.S., Consulting Physician to St. Bartholomew's Hospital; sometime Regius Professor of Medicine in the University of Oxford. Pp. 160. New York: Oxford University Press, 1931. Price, \$2.75.

THE older doctrines of diathesis, dealing with the morbid predispositions of the individual, were largely lost sight of with the rise of bacteriology in the latter third of the last century. More recently the concept "diathesis" is having a glorified rebirth in the doctrine of "constitution," which is being more and more taken into consideration in our study of disease. To quote: "The further nosology is pursued, the more clearly does it emerge that in every case of every malady there are two sets of factors at work in the formation of the morbid picture, namely internal or constitutional factors inherent in the sufferer and usually inherited from his forebears and external ones which fire the train." The author has

developed his theme in a manner that will be found interesting and convincing by the practitioner of medicine, who "wittingly or unwittingly, is constantly engaged in the study of constitutions and predispositions and of reactions to environment."

R. K.

CUTANEOUS X-RAY AND RADIUM THERAPY. By H. H. HAZEN, A.M., M.D., Professor of Dermatology, Medical Department of Georgetown University. Pp. 166; 28 illustrations. St. Louis: C. V. Mosby Company, 1931. Price, \$3.00.

CLEAR, concise statements afford the keynote of this little volume on the therapeutic use of Roentgen ray and radium in dermatology. The material is based upon the author's personal experience with abundant reference to the work of other well-known dermatologists and roentgenologists.

In the first half the principles of irradiation therapy, equipment, technique and the action of radioactive substances are discussed. Of particular merit is the author's emphasis of the vigilance required in protecting the patient and operator against the harmful effects of irradiation.

The rest of the volume deals briefly with the character and amount of irradiation required in specific dermatologic conditions. Here the results obtained by the author and others must prove of inestimable value to workers in this field.

A fair knowledge of Roentgen ray and radium therapy, and of dermatology, is necessary to fully appreciate this book. As a handy reference for the busy radiotherapist this little volume will find its greatest value.

K. K.

BREAST FEEDING. By MARGARET EMSLIE, M.B., CH.B., late Senior Medical Officer for Maternity and Child Welfare, County Borough of Croydon. Pp. 142; 6 illustrations. New York: Oxford University Press, 1931. Price, \$2.00.

THIS is the only book on this subject written by a woman that the Reviewer can recall. Convinced that the preparation for lactation is largely neglected, she devotes a large section to matters such as a high vitamin diet, development and support of the breasts and methods of evertng, elongating and hardening the nipples. The management of breast feeding, its proper inauguration and means of increasing and prolonging the secretion of milk are fully considered. The characteristics of the normal breast-fed infant are explained and contrasted with those of the infant experiencing hunger, overfeeding, colic, vomiting and other difficulties of lactation.

The Reviewer has not found that infants do well on such a small

number of feedings as the author advises, nor does he agree with her that all colic is caused by air swallowing.

This book is in handy form, well arranged, well indexed and provided with a generous list of references. It can be endorsed as a thoroughly convenient and valuable exposition of this important subject, by one qualified for its authorship by a wide experience.

J. S.

BOOKS RECEIVED.

NEW BOOKS.

A Diabetic's Own Cook Book. By STELLA H. LYONS, with a Foreword by LOGAN CLENDENING. Pp. 94. New York: Alfred A. Knopf, 1932. Price, \$2.00.

Cancer. What Everyone Should Know About It. By JAMES A. TOBEY, DR.P.H., with Introductions by JOSEPH COLT BLOODGOOD, M.D., and H. L. MENCKEN. Pp. 323; 17 illustrations. New York: Alfred A. Knopf, 1932. Price, \$3.00.

La Maladie de Boeck. By A. KISSMEYER, Medecin de l'Institut Finsen. Preface by DR. J. DARIER. Pp. 147; 67 illustrations. Copenhagen: Levin & Munksgaard, 1932.

A Text-book of Medicine for Nurses. By E. NOBLE CHAMBERLAIN, M.D., M.Sc., M.R.C.P., Senior Assistant Physician and Cardiologist, Royal Southern Hospital, Liverpool, etc. With a Foreword by Miss E. M. MUSSON, C.B.E., R.R.C., Chairman, General Nursing Council for England and Wales. Pp. 439; 38 illustrations. New York: Oxford University Press, 1931.

Publication on the Costs of Medical Care: No. 10. The Frontier Nursing Service. By ANNE WINSLOW, Executive Secretary, New York Office, Frontier Nursing Service. Pp. 16. Washington, D. C.: The Committee on the Costs of Medical Care, 1931.

Tumors of Bone. By CHARLES F. GESCHICKTER, M.D., Surgical Pathological Laboratory, Department of Surgery, Johns Hopkins Hospital and University, Baltimore, and MURRAY M. COPELAND, M.D., Memorial Hospital, New York City. With Forewords by DEAN LEWIS, M.D., and JOSEPH COLT BLOODGOOD, M.D. Pp. 709; 406 illustrations. New York: The American Journal of Cancer, 1931. Price, \$5.00.

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- Prohibiting Minds.* By STEWART PATON, M.D., Lecturer on Psychiatry, Johns Hopkins University, Baltimore. Pp. 198. New York: Paul B. Hoeber, Inc. Price, \$2.00.
- A Hand-book of Ocular Therapeutics.* By SANFORD R. GIFFORD, M.A., M.D., F.A.C.S. Professor of Ophthalmology, Northwestern University Medical School, Chicago, etc. Pp. 272; 36 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$3.25.
- Clinical Roentgen Pathology of Thoracic Lesions.* By WILLIAM H. MEYER, M.D., Professor of Roentgenology in the New York Post-Graduate Medical School of Columbia University, etc. Pp. 272; 183 engravings. Philadelphia: Lea & Febiger, 1932. Price, \$6.00.
- Traitement de la Tuberculose par la Sanocrysine.* By KNUD SECHER, Medecin-Chef à l'Hospital de Bispebjerg, Copenhagen. Pp. 110; 21 illustrations. Copenhagen: Levin & Munksgaard, 1932.
- Leonardo da Vinci.* By PROF. DR. SIGMUND FREUD, LL.D. (University of Vienna). Translated by A. A. BRILL, Ph.B., M.D., Lecturer in Psychoanalysis and the Psychosexual Sciences, Columbia University. Pp. 130; illustrated. New York: Dodd, Mead & Co., 1932. Price, \$3.00.
- Surgery of the Chest.* By GEORGE F. STRAUB, M.D., F.A.C.S. Pp. 475; 341 illustrations, including 68 color plates. Springfield, Ill.: Charles C Thomas, 1932. Price, \$10.50.
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NEW EDITIONS.

- Recent Advances in Bacteriology.* By J. HENRY DIBLE, M.B. (GLAS.), F.R.C.P., Professor of Pathology in the University of Liverpool. Pp. 476; 29 illustrations. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1932. Price, \$3.50.
- United States Army X-Ray Manual.* Rewritten and edited by LT.-COL. H. C. PILLSBURY, M.C., U. S. A. Pp. 482; 228 illustrations. Second edition. New York: Paul B. Hoeber, Inc., 1932. Price, \$5.00.
- The second edition of this book includes the improvements in apparatus and technic which have been made since the previous publication. The portion devoted to interpretation is well presented.
- Medical Dictionary. II Part, German-English. VI Edition.* By JOSEPH R. WALLER, M.D., and MORITZ KAATZ, M.D. Pp. 238. Wien: Franz Deuticke, 1932. Price, M. 7.—.
- Applied Physiology.* By SAMSON WRIGHT, M.D., M.R.C.P., Professor of Physiology, University of London, Middlesex Hospital Medical School. Pp. 552; 128 illustrations. Fourth edition. New York: Oxford University Press, 1931. Price, \$5.50.
- Manual of Surgery.* By ALEXANDER MILES, M.D., LL.D., F.R.C.S. (EDIN.), Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S. (EDIN. and ENG.), Professor of Surgery, University of Edinburgh. Vol. II. *Extremities—Head—Neck.* Pp. 685; 303 illustrations. Eighth edition. Vol. III. *Thorax—Abdomen.* Pp. 578; 177 illustrations. Eighth edition. New York: Oxford University Press, 1931. Price, \$3.80 each volume.

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UNDER THE CHARGE OF

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The Elimination of Phenolsulphonphthalein by the Kidney.—The Influence of Pathologic Changes in the Liver.—HANNER and WHIPPLE write (*Arch. Int. Med.*, 1931, 48, 598) that many years ago the latter noted that in certain cases of intoxication of pregnancy there was a high degree of elimination of phenolsulphonphthalein by the kidney and suggested that the explanation lay in liver injury. Subsequently it was observed that there was an unusual elimination of phthalein in experimental chloroform poisoning of dogs. These two observations naturally connote hepatic injury modifying the elimination of phthalein. Additional evidence has been brought forth by writers in the more or less recent past to show that the liver can excrete phthalein, the most definite information probably being that of Marsh and Vickers, who recovered 16 per cent of phthalein from the liver of dogs which were killed 15 minutes after the injection of 180 mg. of the dye. The work of Möller and Lundsgaard, furthermore, confirms the hypothesis that the normal liver plays a part in the elimination of phthalein; their work also shows that the dye is observed in the gastro-intestinal tract only in very small quantities. In order to investigate by experimental methods the question of the elimination of phthalein, the two authors poisoned a series of dogs with chloroform by light surgical anesthesia. They also attempted to injure the liver by administration of phosphorus. Injury to the liver was shown by a study of the blood fibrin and the icterus index, as well as by the elimination of phthalein. The second part of the experiment was performed by inserting a cannula into the common duct and collecting the bile and urine for 2-hour periods of time. The flow of phthalein in the bile could not be demonstrated. Control experiments were performed under ether anesthesia and by obstruction of the bile ducts. Elimination of the dye by way of the gastrointestinal tract was determined by feeding 30 mg. of phthalein through the stomach tube to the dog. Only 3 to 5 per cent appeared

in the urine and only traces in the feces, demonstrating the absence of intestinal absorption in the reactions that were studied by the authors. It may be deduced from these experiments, taken *in toto*, that the liver of the normal dog is capable of eliminating through the bile 10 to 15 per cent of the usual dose of phthalein and the surplus, when this way of escape is blocked, appears in the urine, giving very high figures. Not more than 5 per cent of the amount of phthalein that is excreted into the duodenum is reabsorbed. In the dog that has necrosis of the liver produced by chloroform poisoning from 90 to 97 per cent of the dye is eliminated through the kidney as contrasted with the control of from 75 to 78 per cent. The normal figures return when the hepatic injury is repaired. These experiments are of considerable practical value. From time to time excessive elimination of the dye is noted by the clinician who is wont to ascribe this abnormality to some fault of the technic. Hanner and Whipple now show that the explanation lies in pathologic changes in the liver. It is obvious that renal and hepatic disease when combined will disorganize the phthalein test for kidney efficiency. It is likewise obvious that high phthalein elimination indicates liver injury and that the phthalein test may be used as a functional test for liver disease as frequently as it is for kidney disease except that the results from the one are exactly the opposite to the other: high urinary output when there is liver disease; low when there is kidney disease.

SURGERY

UNDER THE CHARGE OF

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Acquired Renal Dystopia or Movable Kidney.—KIDD (*J. Urol.*, 1931, 26, 327) reviews the types of renal dystopia. A fresh hypothesis is formulated which attributes the most important pathologic type to the persistence from neolithic times of a racial stock of Egyptian origin and descent. The importance of the intraabdominal pressure is minimized and the importance of the suspensory ligaments of the kidney are emphasized. The pathology of movable kidney is placed on a fresh plane and is brought into line with the pathology of sprains and deformities. Pyelography is advocated as the only real guide to treatment and as the indicator of the reasons for success and failure of operations. An operation for renal dystopia is described and the points essential for success in operating outlined.

Tumors of the Kidney.—SMITH and FERRIS (*Am. J. Surg.*, 1931, 13, 552) state that they are inclined to feel that these tumors all have a common origin, probably from some prenephric rest, and that the differences are inherently due to the particular reaction of the individual rather than to any fundamental differences in the cells of origin. It is not important clinically to know whether a tumor arises from displaced celomic lining cells or from nephridial rests, except as its clinical behavior varies. In these tumors no inherent differences are apparent in their clinical course, except in degree. Tumors of presum-

able adrenal origin are apt to be slower growing, but may metastasize by the blood stream very early. They perhaps represent slightly more differentiated epithelium than do the tumors of renal origin, but their fundamental cell prototypes are essentially the same, which brings the author to the conclusion that Wilson reached 20 years ago of the underlying mesothelial origin of the entire group. Finally, in reviewing the embryonal tumors of infancy and childhood, the current theory of renal blastoma origin has been accepted. The writers feel that the evidence is sufficient to show that these cells are capable of differentiation even into the bizarre and curious, almost teratoid tumors which we occasionally find. It is but a step from accepting the conception of the origin of embryonal tumors to recognizing that the adult hypernephroma may well arise merely from a later stage of differentiation of the renal blastoma.

The Separate Neural Arch.—WILLIS (*Bone and Joint J.*, 1931, 13, 709) says that the series of 1520 human skeletons at his disposal discloses separate neural arch made by the pedicles, laminae and spinous processes posteriorly in 79, or more than 5 per cent. In vertebral columns with 25 presacrals the incidence is almost twice as great as in columns with the regular 24, but the actual percentage is an accident of the sampling, rather than a criterion of the population at large. Study of the defect, whether unilateral or bilateral, substantiates its essential origin in a skeletal anomaly, and assigns a very minor rôle to trauma. Embryologically the defect falls into the category of anomalous ossifications, of which there are many other examples scattered over the skeleton. It is an anomaly peculiar to the lumbar region and may be found in any lumbar vertebra and on either or both sides, but is usually confined to the last presacral. Thus spondylolisthesis may be a sign of the anomaly. Trauma plays a secondary rôle in this condition, finding the fibrous tissue a point of less resistance to strain than some structure. Separate neural arch in its origin resembles spina bifida, defective articular processes and separate bony centers for transverse mammillary and accessory processes which are peculiarly associated with the lumbar column. It is found more frequently when some other anomaly, such as the twenty-fifth presacral, is present. It is the ultimate result of imperfect ossification whether this be caused by failure in the ossific process itself or by a defect of the preëxisting cartilage.

Split Heel Approach in Osteomyelitis of Os Calcis.—GOENSLEY (*J. Bone and Joint Surg.*, 1931, 13, 759) says that a series of 11 cases of osteomyelitis of the os calcis, 9 pyogenic and 2 tuberculous, have been presented because radical treatment by the split heel or cloven heel method has been eminently satisfactory, there having been no persisting sinuses and but one recurrence to date, the latter occurring in 1 of the cases of tuberculosis. Periosteal stripping and removal of healthy cortical bone is avoided. A minimum of healthy cancellous bone is sacrificed and tunneling is avoided. Sinuses should be disregarded in the incision as they invariably close, providing all dead bone is removed. The plantar scar is so deeply situated that the plantar tissues form two thick cushions well adapted to weight bearing without pain.

THERAPEUTICS

UNDER THE CHARGE OF

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The Influence of Digitalis Bodies on the Pulmonary Bloodflow.—Employing a somewhat modified histamin method, whereby a new cholin derivative was used, PRUSIK (*Ztschr. f. Krebsforsch.*, 1931, 23, 513) presents the results of a series of investigations on the influence of strophanthin or digitoxin on the speed of pulmonary circulation. He finds that where the pulmonary circulation is normal the digitalis bodies exercise little effect. Where it is more rapid than normal, as in uncomplicated Graves' disease, there is a marked tendency for the pulmonary circulation to be slowed both immediately and at the end of 24 hours. On the other hand, in patients with cardiac failure whose pulmonary circulation is slower than normal, the digitalis bodies show a marked tendency to accelerate this circulation, returning it to normal or even temporarily to a rate greater than normal. He compares his results with those reported by Weiss and Blumgart, and calls attention to the fact that his observations were made at shorter intervals of time after single large doses of the drugs, which may account for his more consistent results. He summarizes his findings by saying that the tendency of digitalis bodies is toward a restoration of pulmonary circulation in the direction of normal. That is, its delay where it is overfast and its acceleration where it is too slow.

The Vital Hormone of the Adrenal Cortex.—HARTMAN, BOWEN, THORN and GREENE (*Ann. Int. Med.*, 1931, 5, 539) presents a report upon the actions of the adrenal extract, cortin, both upon experimental animals and upon man. Administration of cortin to adrenalectomized cats maintains them alive and healthy for an indefinite period during which they feel perfectly normal even to the extent of one female's going into heat and becoming pregnant. Its administration immediately after operation also permits the simultaneous removal of both adrenal glands with recovery. Adrenalectomized cats allowed to approach death can be made to recover completely with cortin. The administration of increasing quantities fails to produce signs of overdosage. Its administration to young adrenalectomized rats permits normal growths and development. Cortin also promotes the healing of wounds and raises the resistance of adrenalectomized animals to bacterial toxins. Finally, it raises to normal the resistance to cold which is so greatly reduced by adrenalectomy. In man with adrenal deficiency its adminis-

tration restores the normal contractile power of muscle and raises its resistance to fatigue when tested by the ergometer. One case of a young man with virtually complete loss of adrenal function due to Addison's disease is reported in which the administration of cortin restored health, vigor and nutrition approximately to normal. On withdrawing cortin relapses occurred each of which was controlled promptly by its readministration. After 224 days of maintenance of fair health the patient acquired acute bronchial pneumonia and died. Autopsy proved the presence of great destruction of the adrenals confirming the diagnosis of Addison's disease. A second patient with Addison's disease was observed but died before cortin could be administered in adequate doses. Administration of cortin to a patient with hypothyroidism caused marked restoration of muscular strength without change in basal metabolism or other beneficial effects except a moderate increase in blood pressure. A similar response was observed in the muscular strength of a patient with hyperthyroidism, some improvement was observed in the muscular functions in 2 cases of muscular atrophy and in 1 of muscular dystrophy. Finally, clinical improvement was produced in some cases of severe postinfectious asthenia.

PEDIATRICS

UNDER THE CHARGE OF

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The Hilus of the Lung in the Child.—ALTSCHUL (*Radiol.*, 1931, 17, 1147) believes that the radiologic diagnosis of tuberculosis of the bronchial lymph nodes is not made as often as it should be, especially in children. The width of the hilus does not furnish important evidence for the diagnosis. The density of the hilus is more important than the width. A hilus showing increased density is always questionable, whether there is a general increase of density or of smaller circumscribed foci presenting increased density. In children calcification in the hilus is rare. Great importance should be attached to the comparison of the two hilus shadows. Inequality of the shadows is definite for the diagnosis. In making this comparison one must show both hili in their entire extent, which can be accomplished only by turning the patient about slightly on the body axis. In the majority of cases any enlargement of the lymph nodes is due to tuberculosis. In cases that are not just recent a primary focus of the lung as the starting point of the lymph gland involvement can usually be shown. If such a primary focus cannot be demonstrated it must be remembered that there are other infectious processes that may give rise to the enlarged lymph glands. Often long or short dense strands extend to the hilus, particularly from the lower field. These are due in part to infiltrated lymphatic tracts and in part to inflammatory changes in the connective tissue. Certain groups of lymph glands cannot be shown in the roentgenogram as they fall within the middle shadow. In the absence of positive roentgenographic observation, an involvement of the lymph glands cannot be excluded. The roentgenographic examination in itself

does not suffice for the establishment of the diagnosis and must be supplemented by other clinical methods of examination. The Roentgen ray examination constitutes the most important part of the examination, and without it an accurate diagnosis of hilus involvement is impossible.

Effect of Curd Tension on the Digestibility of Milk.—ESPE and DYE (*Am. J. Dis. Child.*, 1932, 43, 62) found that doubling the curd tension of milk increased the length of the digestive period from 30 to 65 per cent. A normal milk of high curd tension usually means a more concentrated milk than one of low curd tension, and, therefore, one of greater food value. The percentage of casein in the milk seems to be the greatest factor influencing curd tension. The disparagement between soluble proteins and curd tension is even greater. Boiling markedly lowers the curd tension of milk. Acidifying the milk before its coagulation with rennin has the opposite effect as it raises the curd tension. The addition of small amounts of various substances, such as calcium chlorid and sodium citrate, also has a marked effect on curd tension. Diluting milk with water has the same effect on curd tension as diluting it with its own whey. Dilution has a greater effect than merely producing a less concentrated mixture.

Bacillus Mucosus Infection of the Newborn.—JAMPOLIS, HOWELL, CALVIN and LEVENTHAL (*Am. J. Dis. Child.*, 1932, 43, 70) state that an outbreak of infectious diarrhea developed in a nursery for the newborn. Its spread was insidious, and a latent period of two months elapsed after the first few cases appeared. The constitutional symptoms, severe intoxication, dehydration and prostration were out of proportion to the relatively mild diarrheal symptoms. The stools averaged about 6 a day. They were watery and contained mucus but no blood or pus, except in 1 case. The mortality was high in spite of the usual accepted treatment for anhydremic intoxication. Apparently the offending organism was *Bacillus mucosus*, the virulence of which may have been increased by symbiosis with anhemolytic streptococci. *Bacillus mucosus* was isolated from the nasal secretions, stomach contents, stools and intestinal mucosa in a large number of cases. None of the usual organisms causing infectious diarrhea, such as the typhoid-dysentery group, were found. The primary and outstanding pathologic findings in the fatal cases consisted of acute enteritis. The mucous membrane was red, swollen, finely granular and covered with reddish-gray mucus. Microscopic examination showed the mucosa to be infiltrated with polymorphonuclear leukocytes and lymphocytes. A few shallow ulcers were found, and the lymphoid tissue was hypertrophied. There was a relative absence of involvement of the colon, which probably accounts for the comparatively few diarrheal stools and the absence of pus and blood. In only a few instances was there evidence of parenteral infection. In a few babies terminal bronchopneumonia and otitis media developed. *Bacillus mucosus* and anhemolytic streptococci were found in the discharges from the ears and from the lungs. The cultures from the throats of 3 nursery maids gave pure growths of *Bacillus mucosus*, and when these 3 individuals were relieved from duty in the ward the outbreak promptly subsided, and there were no recurrent outbreaks.

DERMATOLOGY AND SYPHILIS

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Lupus Erythematosus Disseminatus.—MOOK, WEISS and BROMBERG (*Arch. Derm. and Syph.*, 1931, 24, 786) present in detail the case histories of 13 patients with disseminated erythematous lupus and while disclosing no new facts their material is a valuable clinical study of 9 fatal cases, 4 of which came to autopsy. In 6 of the fatal cases the duration of the disease was less than 1 year. Remissions were a feature of most of the cases. Leukopenia as an important diagnostic sign and the polymorphism of the cutaneous picture are again stressed. Involvement of the serous cavities was conspicuous in the material studied. The authors feel that insufficient evidence is still at hand to subscribe to the tuberculous etiology so often proposed for this striking and tragic dermatosis.

A Short Review of Alopecia of the Scalp.—PHOTINOS (*Acta Derm.*, 1931, 18, 22) gives the differential diagnosis involved in the clinical evaluation of the scalp alopecias with special reference to the pseudopelade of Brocq, a subject upon which the author has already written a large monograph. Pseudopelade is a type of cicatricial alopecia occurring for the most part in male adults and characterized by small bald patches which have a predilection either for the occiput or the vertex and midportion of the scalp. The number of lesions is in inverse ratio to their size, the smaller the patches the greater the number. Although the patches are irregular in contour they are strictly limited at the borders, which frequently jut out into surrounding parts of the scalp in quite a different fashion from the round and oval lesions of alopecia areata. The hair which may remain within the patches or at the borders is usually normal in appearance although some of it can be easily pulled out, showing a succulent, whitish, glassy sheath. The skin of the patches is white, smooth and atrophic, and slightly but definitely depressed below the level of the surrounding skin. There is a complete absence of inflammatory signs so conspicuous in folliculitis decalvans, a type of cicatricial alopecia resembling pseudopelade except for the presence of follicular pustulation during the active stage. The etiology of pseudopelade is undetermined, the prognosis *nil* for restoration of hair and uncertain for arrest; the treatment, the local use of either sulphur or mercury.

GYNECOLOGY AND OBSTETRICS

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Radium Therapy of Menarchial Hemorrhage.—That type of excessive menstruation which occurs in adolescent girls and which is often termed menarchial hemorrhage has often been a cause of great concern to the gynecologist because in girls of this age conservatism must be the rule except in extreme cases. KELLY (*J. Am. Med. Assn.*, 1931, 97, 760), who was one of the pioneers in the use of radium irradiation in gynecology, presents the results in a series of 30 patients ranging in age from 13 to 25 years who were treated with radium for this condition. In each patient the health was impaired and there was a varying degree of secondary anemia. In 6, the hemoglobin was between 30 and 60 per cent. There were 16 cases in which the period became normal immediately or soon after the treatment and remained so. In 5 there was a temporary amenorrhea with a later return or normal menstruation. There was a group of permanent amenorrhea consisting of 6 cases although in 4 of them sufficient time has not elapsed to be sure of a permanent cessation. He is of the opinion that radium and Roentgen rays find their most brilliant field in the treatment of menopausal hemorrhages, to which most gynecologists subscribe. In the type of cases under discussion, irradiation is also of great value as it usually spares the patient a surgical operation of a radical nature. It is important however, to begin the treatment with the small broken dosage plan and work up through two or three treatments to the efficient amount; in other words, more treatment can always be given when necessary but once an overdose has been given a lasting amenorrhea may be the result. In this series the smallest amount of radiation given was 184 millicurie hours and the largest, 925, the average dose being 583.

Carcinoma of the Ovary.—As a result of a study of a series of cases of cancer of the ovary which were admitted to the gynecological service of Stanford University, EMGE (*California and West. Med.*, 1931, 35, 366) has reached the conclusion that this disease whether primary or secondary, offers a gloomy outlook because of the absence of early symptoms. Menstruation, if still present, may not be much influenced. Pain appears very late and only when the tumor mass has grown to a considerable size or has encroached upon other structures in the pelvis. About half of the patients were disturbed by urinary frequency, dysuria or retention, while loss of weight and ascites are also common symptoms. All of the patients had easily palpable masses while cachexia and secondary anemia, corresponding in degree to the

size of the mass and the metastatic involvement, were noticed in about 60 per cent of the patients. Radical surgery is usually indicated and may be advantageously combined with irradiation with the prospect of prolonging life for a period of 5 years with occasional cures. He has noted no instance in which the removal of a primary ovarian cancer caused the disappearance of metastatic tumors elsewhere. As a matter of prophylaxis, he believes that all newgrowths of the ovary should be removed as soon as discovered regardless of the age of the patient since the percentage of malignant degeneration is high, being 22.8 per cent in this series.

OPHTHALMOLOGY

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The Pathology of Papilledema.—The theories in regard to the pathology of papilledema may be divided into the mechanical and the non-mechanical. The mechanical types may have to do either with a disturbance of the lymph flow or with an interruption of the vascular supply of the optic nerve. The non-mechanical types may be either inflammatory or toxic. Since the discovery by Schwalbe, in 1869, of a connection between the subarachnoid space of the brain and that of the optic nerve, theories of the mechanical origin of papilledema have been supported by experimental work of Schmidt-Rimpler, Manz, Cushing and Bordly, and Schieck. Schmidt-Rimpler believed that there was a direct driving forward of the cerebrospinal fluid through the lamina cribrosa, with an edematous infiltration of the nerve head as a direct result, while the explanation of Manz was based upon compression of the central vessels of the retina as they passed through the lamina cribrosa. Cushing and Bordly corroborated this work. A different type of explanation was advanced by Schieck who believed the condition was caused by the entrance of the cerebrospinal fluid under increased pressure in the preformed perivascular lymph spaces of the axial bundle of the optic nerve and along the central vessels into the disk. The position of the central vein in the optic nerve determines the amount of compression of the perivascular lymph spaces and has been studied by several investigators. Fry (*Am. J. Ophthalm.*, 1931, 14, 874) examined a series of 40 eyes obtained from 21 cases. In 17 of the cases the diagnosis was brain tumor, in 2 of the cases meningitis and there was 1 case of brain abscess, 1 of gumma of the brain and 1 aneurysm. In 32 of the eyes examined there was a papilledema present and all but 2 of them the condition was recent. The average swelling was $3\frac{1}{2}$ diopters. The course of the central artery and vein as they leave the nerve was studied to determine where

pressure occurred along the course of the vessel that could result in the edema of the nerve head and nerve fiber layer of the retina. This compression was found to occur in the subarachnoid space in 62 per cent and in the side of the nerve in 38 per cent of 26 eyes showing papilledema. Compression of the nerve was found in 84 per cent of 31 eyes showing papilledema. The evidence was in favor of active compression of the central vein by an increased fluid pressure within the nerve pressing forward into the eye. Fry believes that the edema of the nerve head which produced the characteristic ophthalmoscopic appearance of choked disk occurs also in the subpial portion about the central vessels in the nerve stem. The diameters of the nerves, anterior and posterior to the entrance of the central vessels, were the same in 6 cases, and in 1 the diameter posterior was greater. In the remaining 17 instances the anterior diameter was greater, showing the greater amount of edema anteriorly. Evidence of inflammatory change as a cause for papilledema could not be found. The initial cause of papilledema is a compression of the central vein of the retina along the side of the nerve or in the subarachnoid space. This produces a venous stasis with a consequent transudation of lymph into the tissue of the optic disk and adjacent nerve fiber layer of the retina. The secondary cause is a forward pressure of fluid within the optic nerve, produced in all probability by the infiltration of cerebrospinal fluid under increased pressure in the perivascular lymphatic spaces.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Noises of Civilization and Their Evil Effects.—Largely by utilization of tools has man become differentiated from other animals. It was inevitable in this "age of machinery" that noise should increase. WELLS (*Ann. Otol., Rhinol. and Laryngol.*, 1931, 40, 143) roughly classifies the world's noises as originating from such causes as: animate nature; war; building and construction; traffic and transportation; manufacture; commerce, and communication. After discussing the various types of noises, qualitatively and quantitatively, the author states that the deleterious effects of noise may fall chiefly on the auditory apparatus, *per se* or on the general nervous system. The hearing organ may be affected: (1) By loss of function; (2) by developing abnormal sensitivity, or (3) acquiring a tolerance, to the noise.

It is a fundamental physiologic law that an organ exposed to excessive stimuli must either adapt itself thereto or suffer harm. Phylogenetically, as the youngest of our special senses, audition is frailer than any of the others. Noise deafness is not unduly common and ordinarily results from long continued contact with high-pitched, intense, disagreeable and annoying noises—as in the well-known boiler-maker's deafness. The impaired hearing of aviators is due to

noise and often also to tympanic lesions from other obvious causes. Railroad engineers, miners, "sand hogs," riggers, etc. also get "nerve deafness," which however is due more to concussion than to noise. Following a philosophic discussion Wells, concludes ". . . or will not science find some effectual means to rid us of this unwholesome by-product, so that civilization may eventually reach the goal which is its aim?" (rest and quiet).

Concussion Deafness of Miners With a Survey of the Motor Apparatus in Modern Mines.—For the purposes of his presentation, KATZCHINANN (*Ztschr. f. Laryngol., Rhinol.*, 1931, 20, 353) distinguishes between deafness due to noise and due to vibration (concussion). Moreover, "concussion" is employed in the sense of continuous, multiple, corporeal vibrations rather than a sudden explosion (usually causing rupture of the ear drum) or a cranial injury with *concussio cerebri* or tympanic and labyrinthian trauma.

This vibration or concussion deafness, as interpreted by the author, occurs oftenest in workers subjected over a long period of time to incessant and rapid vibrations, with or without excessive noises—notably in railroad engineers, miners, riveters, riggers, etc. In miners the condition appears to have arisen since the introduction of compressed-air or motor-driven machinery. The lesion is essentially one of the auditory perceptive apparatus. An attendant "rushing, hissing or humming" tinnitus makes the miner "irritable, apprehensive, and suspicious." Both the deafness and the tinnitus increase the underground miner's liability to accident; and is obviously, therefore, of medicolegal importance. Vertigo is absent, the vestibular organs apparently escaping. Like any other occupational disability, the treatment is prevention. The technicalities of mining machinery is discussed.

RADIOLOGY

UNDER THE CHARGE OF

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Roentgen Treatment of Chronic Leukemia.—MCALPIN, GOLDEN and EDSAL (*Am. J. Roent. and Rad. Therap.*, 931, 26, 47) relate their experience with Roentgen treatment in 24 cases of myeloid leukemia and 23 of lymphatic leukemia. In the first group 18 patients died after an average illness of 3 years, and 5 are living but with a shorter average illness. In the second group 16 patients died after an average illness of 1 year 6 months, and 5 are living with an average of 4 years 6 months. These writers maintain that every patient is more or less an individual problem. A blood count should be made before each treatment. Small doses of Roentgen rays to the enlarged nodes and spleen in the

lymphatic type, one area at a time, and to the spleen in the myelogenous type, are advised. The patient should be treated regularly, at first every week; later the period may be lengthened when the response and susceptibilities of the patient have been established.

Criteria of Acute Intestinal Obstruction; Value of Roentgen Ray Evidence.—Intermittent, crampy, colicky pain, associated with nausea and vomiting but unattended by local physical findings, suggests acute intestinal obstruction, says WANGENSTEEN (*Radiology*, 1931, 17, 44). Shadows of gas in the small intestine demonstrate the presence of intestinal stasis. The "ladder pattern" of gas distention in the small bowel need not be awaited to make the diagnosis. In simple obstruction gas can usually be visualized in the small bowel within 4 or 5 hours after the onset of symptoms. When the obstruction is due to strangulation the gas does not appear as early as in simple obstruction. In the inhibitive ileus of peritonitis, gas distention of the small bowel may be observed early. Distention of both colon and small intestine is almost invariably present. Dense "bands" between the intestinal loops are indicative of exudate between the intestinal coils.

Osseous Changes in Hyperparathyroidism.—Roentgenographic changes observed in the osseous system in 2 cases of hyperparathyroidism associated with tumor of the parathyroid gland are described by CAMP and OCHSNER (*Radiol.*, 1931, 17, 63). The roentgenographic changes comprise generalized osteoporosis, cystic lesions and deformities. The generalized osteoporosis is characterized by a miliary or granular appearance, is best observed in the skull, and seems to be peculiar to hyperparathyroidism. In addition, the trabeculae and cortical bone are thinned, and areas of subperiosteal absorption are seen in the long bones and phalanges. Single or multiple cystic lesions are found in the jaw, pelvis and long bones, and are often confounded with those of osteitis fibrosa and giant-cell tumor. The deformities caused by softening of the bones consist of kyphosis, narrowing of the pelvis, coxa vara, bowing of the legs, and infractions. Renal calculi are not uncommon. In each of the 2 cases removal of the parathyroid tumor was followed by definite arrest of decalcification and progress toward restoration of the normal bone structures.

Physical Therapy Measures in the Treatment of Burns.—In the treatment of extensive infected burns, PECK (*Arch. Phys. Therap., X-ray, Rad.*, 1931, 12, 327) has found heat and ultraviolet radiation to be valuable aids to skin-grafting. The heat, applied after grafting, was derived from an "oven baker," and a temperature of 100° F. was maintained about the injured parts, which were kept covered by moist dressings. Ultraviolet radiation was used in preparing the wound surfaces for grafting. It appeared to decrease the amount of surface infection and to promote more rapid formation of healthy granulation tissue. When the infection was marked, an initial exposure of 100 to 150 per cent of the erythema dose was given, and this was followed by smaller doses. After about 2 weeks the wound was ready for skin-grafting, and the heat treatment was then also supplemented by renewed ultraviolet radiation.

NEUROLOGY AND PSYCHIATRY

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Stuttering.—BLANTON (*Ment. Hyg.*, 1931, 15, 2, 270), states that speech is the index of the mind; not only the index, but the very medium through which the mind is formed and developed. No child should leave school with a defect of speech if it is possible to remedy it. Stuttering, especially, should receive the attention of teachers everywhere, for it not only causes a blocking or hesitations in the outward speech, but disturbs the emotions so that clear thinking is often impossible. It may show itself as a complete blocking of the speech or a repetition of initial sounds is any imaginable combination of these two symptoms. There is no dividing line between the frank stuttrer who shows blocking and hesitation, and the person who is nervous, embarrassed, and timid when called upon for speech. Speech is a medium of group social adjustment. Stuttering is a symptom of an inability to adjust to the group. It is caused by a fear, a timidity, or a negative (hate) attitude toward the group. To understand the cause of stuttering in an individual, it is necessary to study first, the development of the emotional life of the stuttrer and second, the nervous and muscular system of this person. Psychoanalysis alone, is not an effective method of treating stuttrers. Speech training must also be used in most of these cases to get adequate results. The physical symptoms of stuttering are explained by the fact that speech is made up of muscle movements that have a more primitive function. Breathing movements, chewing movements, suckling movements, coughing, and vomiting movements, are all coordinated through the speech area into the unified movements of speech. When there is an emotional blocking of the control of the higher brain centers over these lower brain centers, each lower brain center tends to act independently, but it is the early fixations that determine whether the stuttering shall consist of a repetition of sounds, or a vomit-like blocking, or a suckling movement. The psychologic causes that lie back of stuttering—the fixation of the libido at the oral, or anal-erotic stage and at the narcissistic stage, make the stuttrer so sensitive to the attitude of others that he is often unable to speak normally. Other causes of stuttering are left-handedness, and developmental defect of organic, constitutional or functional nature in the muscular and nervous system underlying speech. The treatment of stuttering comprises physical hygiene, mental hygiene, and speech training—each of which the author discusses quite adequately and in a well-rounded manner.

On the Treatment of Tabetic Optic Nerve Atrophies With Sulphur.—WINKLER (*J. Nerv. and Ment. Dis.*, 1931, 73, 276) declares that optic nerve atrophy of tabes is characterized by: (1) Disappearance of the most tender septal ramifications and of their bloodvessels, then a club-shaped thickening of the bigger septa; (2) the glia fiber system, mediating for the nourishment of the nerve fibers from the bloodvessels, first shows a spotty sclerotic thickening and will disappear later; (3) the sheaths of the nerve fibers tumefy at the center, later are destroyed and secondarily destroy the axon itself. In the pathogenesis of the optic atrophy the nutritive trouble caused by the destruction of the glia and the capillaries must play the leading rôle. To this is added a toxic action. Assuming this to be correct, then only such a therapy can be successful, which beside improving the blood and lymph circulation of the optic nerve, will also promote the elimination of the spirochetal toxin by neutralization or by a rapid transportation from the organism, and will raise the resistance of the nervous glial elements against these toxins, vivifying the intermediary metabolism and also the elimination of the local toxin. This therapy is adequately supplied by intramuscular injections of sulphur. After treatment the changes noticed are: (1) Improvement of visual acuity; (2) enlargement of the visual field; (3) reappearing of color vision, and (4) changes of the grayish discoloration into red, due to improved circulation. The observed result has proved permanent to the present time.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Pulmonary Asbestosis in a Dog.—SCHUSTER (*J. Path. and Bact.*, 1931, 34, 751) reports the autopsy findings on a dog which had lived 10 years in an asbestos factory. The animal had had dyspnea for the last 2 years of its life, lost considerable weight, and was finally killed as it became helpless. The lungs were small and showed a diffuse shotty induration. The pleura was markedly thickened. There was no evidence of pneumonia, hemorrhage or tuberculosis. The author regards the lung changes as an uncomplicated picture of asbestosis, characterized by an interstitial fibrosis, dilatation of bronchioles and the presence of numerous asbestos spicules. "Asbestos bodies" (described by COOKE, *Brit. Med. J.*, 1927, 2, 1024) were lacking in the lungs of this dog. The author regards these bizarre formations as the product of infection superimposed upon asbestosis.

The Anticarcinogenic Action of Dichlorodiethylsulphid (Mustard Gas).—BERENBLUM (*J. Path. and Bact.*, 1931, 34, 731) reports the results of further experiments along the same lines as his earlier work on mice showing that mustard gas inhibits the tumor producing properties of tar, from which the author concludes that mustard gas exerts a purely local action upon the mouse skin causing it to become refractory to the carcinogenic action of tar. This refractory state develops almost as soon as the mustard gas treatment is begun and subsides very soon after this treatment is discontinued. No distinctive histologic changes could be attributed to the mustard gas, a fact which inclines the author to abandon his earlier view that the tumor inhibition was due to a "superoptimal degree of irritation." He now suggests that mustard gas may exert some specific chemical action on the tissues rendering them refractory to the carcinogenic properties of tar.

Flocculation Reaction With Staphylococcal Toxin.—BURNET (*J. Path. and Bact.*, 1931, 34, 759) studied the flocculation phenomenon that occurs when staphylococcal toxin and antitoxin are mixed under certain conditions. The author found that this reaction in many respects was similar to that obtained with diphtheria toxin. Flocculation actually represented a precipitation of the product of toxin-antitoxin union for, by suitable methods, either toxin or antitoxin could be liberated from the washed floccules. The point of optimal flocculation was found to be constantly related to the tube in the mixtures that contained equal quantities of toxin and antitoxin but it always occurred in the zone, from this neutral point, of excess antitoxin. The point of optimal flocculation did not indicate a "natural" equivalence of toxin and antitoxin. The flocculation of toxins modified by formalin treatment and by heat was also described and compared with the other properties of such preparations.

Blood Cultures in Chronic Infectious Arthritis.—BERNHARDT and HENCH (*J. Inf. Dis.*, 1931, 49, 489) endeavored to confirm the finding of CECIL, NICHOLLS and STAINSBY (*Am. J. Med. Sci.*, 1931, 181, 12) that streptococci could be isolated from the blood stream of patients suffering from chronic infectious arthritis in 62.3 per cent of cases. A survey of previous bacteriologic studies was made and 780 cases collected, microorganisms had been isolated in 26 per cent of these, with streptococci forming 18 per cent. Twenty patients in the active stage of rheumatoid arthritis afforded the material for the present investigation. Blood culture was carried out for 30 days by three different methods, including that published by Cecil, Nicholls and Stainsby. The media used by the latter writers had, however, been fractionally steam sterilized while that used by the authors was autoclaved. Contrary to the results quoted above, streptococci were not found in any of the cultures. Growths were obtained from 5 of the patients, 4 were staphylococci and the fifth a diphtheroid organism. The authors do not consider their results as an argument for or against the infectious theory of this type of arthritis, but point out that it is extremely difficult, with present cultural methods to isolate microorganisms from the blood of people suffering from the condition studied.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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An Epidemiologic Study of Typhoid Fever in Six Ohio River Cities.—VELDEE, (*U. S. Pub. Health Rep.*, 1931, 46, 1460) points out that the sanitary control of the public water supply is for the purpose of preventing water-borne diseases, especially typhoid fever, and the pollution of the raw water of the Ohio River is notorious. It is shown that prior to purification the typhoid rate was very high and that the disease occurred throughout the year. After purification of supplies was inaugurated the disease was much reduced and became one limited to summer and fall. In the opinion of the author it can no longer be attributed to water.

Cultivation of Vaccine Virus for Jennerian Prophylaxis in Man.—RIVERS in a previous communication has described a simple medium for the cultivation of vaccine virus. The results of the work reported at that time clearly indicate that vaccine virus is capable of multiplication in the presence of minced chick embryo tissue suspended in Tyrode's solution. The experiments, however, were conducted with a neuro-vaccine virus and, although the active agent engendered in cultures caused typical vaccinal lesions in rabbits, it was deemed best not to test it in human beings. To obtain a culture virus for Jennerian prophylaxis in man it seemed advisable to adapt a dermal strain of vaccine virus to the particular method of cultivation. The present paper (*J. Prev. Med.*, 1931, 54, 453) deals with the results of this work. The medium employed for the *in vitro* cultivation of vaccine virus is exceedingly simple, but one must remember that it contains living cells. In spite of recent reports to the contrary, no one has definitely shown that vaccine virus is capable of pollution in the absence of surviving susceptible cells. Several kinds of media have been devised for the production of vaccine virus. The one described in this paper, however, is the best of the lot already proposed, because, inasmuch as neither serum nor plasma is used, and since the tissue consists of minced chick embryo, it is the least likely to become contaminated by an extraneous virus injurious to man. Furthermore, the virus produced in this manner remains potent in 50 per cent glycerol at $+2.5^{\circ}$ C. for at least a month. More information, however, concerning the length of time the culture vaccine remains active under a variety of conditions should be obtained, and to this end experiments are now being conducted. A dermal strain of vaccine virus has been adapted to a simple culture

medium consisting of minced chick embryo suspended in Tyrode's solution. The bacteria-free culture virus thus obtained produces in lower animals and in man typical vaccinia that renders them refractory to infection with ordinary vaccine virus harvested from calves.

The Effect of Irradiation With Ultraviolet Light on the Frequency of Attacks of Upper Respiratory Disease (Common Colds).—DOULL, HARDY, CLARK and HERMAN (*Am. J. Hyg.*, 1931, 13, 460) report the results of studies of a group of adult volunteers, numbering 363, who were kept under observation from September 29, 1929, to May 31, 1930, a period of 35 weeks. A vigorous effort was made to secure reports of all cases of upper respiratory disease (common colds). From this number, approximately one-half was selected at random for irradiation, which was given over the first 31 weeks of the period. Mercury-vapor lamps were used and the intensity of erythema-producing rays was measured biweekly. The dosage was light to moderate, the individuals being stripped to the waist and exposed, either on chest or back on each occasion, to that dose, which from previous experience with the subject, seemed likely to produce only a minimal erythema. Total incidence for the period was slightly higher for the irradiated (receiving more than 10 treatments) than for the controls. Also cases of a more severe type, as evidenced by absence from duty and confinement to bed, by occurrence of fever, by productive cough or by long duration, were just as frequent in the irradiated as in the control group.

The Weil-Felix Reaction in Endemic Typhus Fever and in Rocky Mountain Spotted Fever.—SPENCER and MAXCY (*U. S. Pub. Health Rep.*, 1930, 45, 440) refer to the fact that the Weil-Felix reaction has been regarded as highly specific of typhus. After a description of the cultures and technique they state the following conclusion: The Weil-Felix reaction is positive in a large proportion of cases of Rocky Mountain spotted fever. The mechanism of this reaction, although similar, is not exactly identical with that occurring in typhus fever. There is a qualitative difference.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 23, 1932

Evidence for the Existence of Amino Groups on the Serum-sensitized Surface.—ELEANORE W. JOFFE and STUART MUDD (from the Department of Bacteriology and the Henry Phipps Institute, University of Pennsylvania). The combination of antigen and antibody is dependent upon the specific chemical constitution of both substances. This combination forms or results in the formation of a deposit or film on the

antigen surface. The properties of this sensitizing film approximate those of denatured serum globulin.

The specific combination between antigen and antibody may be determined by agglutination or by the resuspension reaction. These reactions are consequent upon the deposit of antibody globulin on the antigen surface. With the progressive formation of a surface deposit, the isoelectric point of the antigen particles approaches that of the deposited substance. This affords further means for demonstrating that specific combination has taken place.

The addition of formaldehyde in sufficient excess to a protein masks the presence of any primary amino groups and leaves the protein with freely titratable carboxyl groups. Such a deamination should shift the isoelectric point of the protein to the acid side.

This report presents evidence for the existence on the serum-sensitized surface of free primary amino groups which can be substituted without very greatly interfering with the combination of antibody with antigen.

Salmonella pullorum was sensitized with specific antiserum. When sensitization was complete, the sensitized bacteria were divided into two portions. One of these was treated with saline solution, the other with formaldehyde. Agglutination and resuspension reactions were read. The isoelectric points were determined in the microcataphoresis apparatus. The isoelectric point, in the case of maximally sensitized bacteria, was shifted from $\text{pH} = 5.2 - 5.0$ to $\text{pH} = 4.5 - 4.3$. In order to determine whether specific combination would take place if the serum was first deaminized, the specific antisera were treated with formaldehyde. The bacteria were then added (1) suspended in salt solution, and (2) suspended in formalin. Agglutination and resuspension reactions were read. The isoelectric points were determined and found to fall within the range $\text{pH} = 4.5 - 4.3$ in maximal sensitization.

Previous experimental work has shown that most bacteria migrate to the anode when placed in a buffered solution in an electric field. In some cases the bacteria have definite isoelectric points, whereas others retain a negative charge even down to pH values below 2.0. The strain used in the experiments described show only a minimal charge in buffers of any pH studied and this minute charge is not altered by treatment with formaldehyde. With sensitization this organism assumes a definite isoelectric point and this isoelectric point does not vary greatly as sensitization increases.

Thus the shift in the isoelectric point due to treatment of the sensitized bacteria or of the antiserum with formaldehyde does not seem to be due to a removal of antibody globulin film from the antigen but to an alteration in the chemical nature of the film. This alteration is interpreted as an effect upon primary amino groups in the serum-sensitized surface.

Estimations of Cardiac Work During and After an Attack of Angina Pectoris.—ISAAC STARR, JR., LEON H. COLLINS, JR., and FRANCIS C. WOOD (from the Medical Division of the Hospital of the University of Pennsylvania and the Laboratory of Pharmacology, University of

Pennsylvania). We have been fortunate enough to secure observations on a case of angina pectoris during an attack. Before the attack blood pressure and pulse rate were normal. After the onset of pain, pulse rate and blood pressure increased markedly and respiration was recorded as high. At this time the cardiac output (Starr and Gamble method) was 3.4 liters per min., the cardiac work 6.6 kg. meters per min., the cardiac work per beat 52 gm. meters, the oxygen consumption 200 cc. per min. Twenty minutes later the pain was far less intense, the blood pressure had fallen somewhat, the pulse rate and respiration were also lower. The cardiac output was 2.4 liters per min., the cardiac work 3.6 kg. meters per min., the cardiac work per beat 36 gm. meters, the oxygen consumption 173 cc. After these determinations nitroglycerin was administered and the pain disappeared within 5 minutes. The pulse rate did not change significantly, the systolic blood pressure fell a little but regained its previous level in a few minutes; diastolic pressure and respiration were unchanged. Fifteen minutes after the drug the cardiac output was 2 liters per min., the work 2.5 kg. meters per min., or 28 gm. meters per beat, the oxygen consumption 188 cc.

These data are consistent with the conception that angina is caused by a situation which demands increased cardiac work, for the work decreased as pain diminished. On the other hand they do not seem consistent with the conception that angina is primarily due to coronary spasm, for in this condition one would expect the work of the heart to be diminished during an attack and to increase after it was over.

About two weeks after these observations the patient had an attack diagnosed as coronary occlusion and died. Necropsy was not permitted.

Absorption of Oxygen by the Skin and Its Effect Upon the Vascular Reaction to Stasis and to Histamin.—S. GOLDSCHMIDT and B. MCGLONE (from the Department of Physiology, University of Pennsylvania). The cyanosis, which develops in an arm with the circulation totally or partially occluded, may fail to appear when the part is surrounded by an atmosphere of oxygen. This result is a convincing evidence of the passage of oxygen through the skin into the blood of those vessels which give it color, and is consistent with the findings of previous investigators, notably Shaw and his coworkers,¹ that oxygen may be absorbed by the cutaneous route. The skin of the forearm is usually maintained free of cyanosis under these conditions, while the fingers especially and the hand are quite refractory.

Reactive hyperemia upon release of the occlusion is confined to those parts which were cyanosed or "dusky" before the release. The oxygen, therefore, would seem to prevent the dilatation of the skin vessels which prevails in an arm with arrested circulation, in air or nitrogen.

The failure to obtain a reactive hyperemia under these conditions was examined in the light of the hypothesis of Lewis,² which ascribes the control of the small vessels of the skin to an "H" substance, a normal metabolite, the identity of which with histamin Lewis believes to be established by a wealth of convincing evidence.

Our findings, therefore, would seem to indicate that either histamin is not produced or it is destroyed under the prevailing conditions. The idea as developed by Lewis precludes the first possibility, since if one

assumes that dilatation of the small vessels of the skin under a variety of physiologic conditions is due to the "H" substance, one must of necessity, as indeed Lewis does, postulate that the substance is a normal skin constituent, present in but small amounts normally, but piling up when the circulation is arrested.

As to the second possibility, a destruction of the histamin by the high oxygen tension, it might be expected, if this were the explanation of our findings, that there would be a diminution or failure of the histamin reaction when introduced intradermally. On the contrary, the reaction is obtained even in very high dilutions. Indeed, under these conditions one observes a well defined flare, a fact also incompatible with Lewis' belief that this part of the "triple reaction" of histamin is exclusively a reflex arteriolar dilatation.

1. Shaw, L. A., Messer, A. C., and Weiss, Soma: *Am. J. of Phys.*, 1929, 90, 107.
Shaw, L. A., and Messer, A. C.: *Am. J. of Phys.*, 1930, 95, 13.
Shaw, L. A., and Messer, A. C.: *Am. J. of Phys.*, 1931, 98, 93.
 2. Lewis, Thomas: *The Bloodvessels of the Human Skin and Their Responses*, London, 1927.
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The Nervous Discharge from the Carotid Sinus.—D. W. BRONK and G. STELLA (from the Johnson Foundation for Medical Physics, University of Pennsylvania). A large body of evidence emphasizes the importance of afferent nerve impulses from the aorta and carotid sinus in the nervous regulation of blood pressure. There is, however, little known regarding the nature of these nerve messages and how they effect this regulation. The present study has therefore been directed to an analysis of the discharge from single pressure receptors in the walls of the carotid sinus in relation to the arterial pulse.

Synchronous with the rapid systolic rise in pressure the end organ discharges impulses at a maximum frequency that may be as high as 120 to 140 a second. If the mean pressure is not high, the frequency rapidly falls during diastole and in many cases there is no discharge of impulses at all during this part of the cycle. The frequency and duration of the discharge is, however, largely dependent upon the form of the pulse curve and the mean pressure.

As the mean blood pressure increases, the average frequency of impulses increases, the duration of the discharge in each heart cycle becomes longer and more end organs come into action. The result of a higher blood pressure is therefore a greater number of afferent impulses going to the centers in the medulla per unit of time. This increased number of impulses presumably acts upon the vasomotor centers in such a way as to cause a decrease in the outflow of sympathetic impulses to the walls of the bloodvessels, with a consequent vasodilatation and fall in pressure.

The Association of Duodenal Ulcer With Adrenal Damage.—CHARLES McLAUGHLIN (from the Department of Research Surgery, University of Pennsylvania). Observations from 19 dogs with varying degrees of adrenal injury were reported. Ten of these were subjected to bilateral adrenal damage, while 9 had only one adrenal injured. Cauterization

of the adrenal cortex, and to a lesser extent of the medulla, has been undertaken in two stages, using a high frequency coagulating current. A period of from 2 to 3 weeks was permitted to elapse between operations. The average time elapsing between the first operation and autopsy, of the group subjected to bilateral cauterization, was $31\frac{1}{2}$ days. The period before autopsy following the second stage of the procedure varied from 1 to 10 days.

Congestion involving the mucosa of both the stomach and small bowel was noted in 5 cases, being moderate in degree in 3 animals and marked in 2. Congestion of the mucosa of the small intestine alone was much more striking, being present in 10 dogs. Frank gastrointestinal hemorrhage with free blood in the stomach and small intestine was present in 3 dogs. In 15 of the animals definite ulceration was present in the small intestine, being most marked in the duodenum, but present also in the jejunum and upper ileum. In no case was any evidence of gastric ulceration found.

The ulcers were of two distinct types, which we have classified as acute and chronic on the basis of their appearance. In 8 animals the ulceration was of the acute type. The average length of life following the first stage of the operative procedure in this group was 15 days, only 4 of these 9 dogs having been submitted to the second stage operation, so that in 5, only one adrenal was affected.

Seven of the 15 animals presented definite circumscribed ulcers of a chronic type, with heaped up edges and ragged excavated craters. The ulcers appeared in the duodenum, jejunum and upper ileum, from 3 to 8 being found in each animal. No ulcers were ever present above the pyloric ring although in several animals they began just distal to it. There was no evidence of perforation in any case. The average length of life in this group of 5 animals following the first operation was 29 days.

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ORIGINAL ARTICLES.

PERORAL AND INTRAVENOUS CHOLECYSTOGRAPHY:
A COMPARISON OF THE RELATIVE MERITS AND
RESULTS IN 100 CASES.*

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THE following study is an attempt to determine from the clinical as well as roentgenologic standpoint the relative effectiveness in cholecystography of the two accepted methods of administering the iodine-containing dye; incidentally to establish for ourselves the practicability of the intravenous method for ambulant patients.

The study differs from previously reported comparisons in that the patients were chosen to represent all phases of the gall bladder syndrome. Practically all results heretofore reported have been obtained incidental to a larger series in those individuals who came to operation, and by investigators who were already committed to one or the other method of administration. The reports have shown fairly consistent agreement in positive findings in the obviously diseased gall bladder which demands surgical treatment; and the operation has confirmed both the peroral and intravenous tests in upward of 80 per cent of instances.

The clinician's real problem in gall bladder suspects, however,

* Read before the Section on Medicine of the College of Physicians of Philadelphia, March 23, 1931.

is to determine accurately when to advise surgical treatment in the instances in which symptoms and signs have not yet indicated surgery to patient and doctor alike. If taken in the elective stage, operation obviously prevents much suffering and secondary morbid change in the body. The real diagnostic value of cholecystography therefore lies in its dependability in these less dramatic cases. Consequently, the present series was made to include a majority of mild or indefinite cases in spite of the fact that operative proof was not obtained. In the absence of operation we have checked the accuracy of the two tests against the assembled clinical data and final diagnosis.

Further unprejudiced comparison of the value of the tests is indicated also by the fact that in the 7 years that cholecystography has been in use a distinct cleavage has developed between proponents of the peroral and intravenous methods. The originators¹ and a large number of able examiners use the intravenous technique exclusively. An equally imposing group of clinicians and roentgenologists maintain the superiority of the peroral method.

The former group have consistently held that the unreliability of the peroral method outweighs in importance the technical difficulties of the intravenous. Their position is that the peroral test is of value only if it shows normal gall bladder function, the presence of nonopaque cholesterol stones, or gross deformities of the viscus. In the instances in which the shadow is faint or absent from the roentgenographic films they contend that the interpreter frequently cannot be certain whether gall bladder or test is at fault. The doubt arises from the fact that imperfect absorption of the dye from the intestinal tract, or vomiting or diarrhea which at times follow its ingestion, may play a part in the abnormal result. Asserting that the above variables cannot be eliminated when the dye is given by mouth, and because they are likely to implicate a gall bladder not diseased, that school subordinates the practical difficulties of the intravenous technique to a determination to achieve accuracy.

On the other hand, the proponents of the peroral method feel as strongly that, with proper technique and watchfulness, its unreliability may be minimized; that its simplicity and harmlessness make it therefore the method of choice, especially where large numbers of patients must be handled.

One further factor, that of reaction to the drug, must be considered in an appraisal of the methods. Reactions to the swallowed dye, while they may interfere with the interpretations, are never alarming. Serious or dangerous reactions, on the other hand, have been reported when the dye is injected into a vein. Such have been denied for a large series by Moore² who reported recently the experience of 6½ years at St. Louis. Kirklin³ of The Mayo Clinic, however, who uses the peroral technique, in a recent appraisal of cholecystography, writes: "Occasional serious reactions, even in the

hands of experts, make one hesitate to urge its use (*i. e.*, the intravenous method) as a general routine. . . . Few examiners use it in office practice; the general feeling is that the patient should be hospitalized." Such requirement would of course seriously handicap the intravenous method as a routine measure.

Methods. Our procedure was to choose, during the past year, as they came along for study, 100 patients from the gastrointestinal outpatient section and the medical wards of the hospital, and arrange that each one receive both tests as closely together as possible. Sixty per cent of the group were chosen from among the outpatients in order to establish to our satisfaction that the intravenous test is safe and practicable for ambulant patients. This of course is an absolute necessity if the intravenous method is to compare in practical value to the peroral. Seventy of the patients were women, 30 men. All but 10 received the dye by mouth first. (It was found that the order of the tests had no influence on the interpretations). Most of the patients were gall bladder suspects. In 15 per cent biliary tract disease was not seriously considered and these individuals acted as controls. We excluded from the intravenous group, and therefore from the series, only those patients with marked cardiovascular disease, in whom reaction or sudden fall in blood pressure might lead to accident, and patients in the acute stage of cholecystitis or with common duct obstruction, in whom both tests are valueless.

No modifications of the established technique were made which might alter the interpretations of one or the other test. The department of radiology had previously set 40 gr. (2.6 gm.) of tetiothalein sodium N.N.R. (Iodeikon-Mallinckrodt) as the standard dose of dye adequate for satisfactory shadows by the peroral route. It was given dissolved in water with or shortly after a light evening meal. The first film was made 14 hours later. Tetradol and other preparations had been given thorough trial by the department and no other found so uniform in results. Grape juice as a vehicle had been discarded because it was found often to cause pylorospasm and slow absorption; carbonated water, because some of the dye was apt to be lost in the froth which resulted from the mixture. Data regarding the relative amounts and types of dye used are included in Table 1.

TABLE 1.—METHOD OF STUDY.

	Number and per cent.
Total number of cases studied	100
Interval between tests: Less than 3 weeks	81
3 weeks to 3 months	9
Over 3 months	10
Dye used: Peroral method:	
Tetiothalein-sodium (Iodeikon), 2.5 gm.	100
Intravenous method:	
Phentetiothalein-sodium (Iso-iodeikon), 2.5 gm. . . .	88
Tetiothalein-sodium (Iodeikon), 3.5 gm.	12

For the intravenous test the patients reported in groups of 2 or 3 in the late afternoon. We found for this work, after a trial in 12 cases of the identical dye used for oral administration, that the isomer of tetraiodophenolphthalein, the phentetiothalein sodium N.N.R., or iso-iodeikon, was the more satisfactory. The dye was injected and the effects closely watched for $\frac{1}{2}$ hour by one of us (L. H. H.).

We further diluted the freshly sterilized 8 per cent solution of the drug by injecting it, not directly into the vein, but into the rubber tubing through which a free gravity flow of warm physiologic saline into the vein had been established. This refinement was first suggested by Liest⁴ and to us by Dr. Jacob Vastine. By such procedure we hoped to escape the severe reactions which are generally believed due to too rapid administration or too strong a solution.

Each subject was kept recumbent for at least $\frac{1}{2}$ hour after the injection and then allowed to go home or back to the ward as the case might be. Sixteen to 17 hours elapsed between the injection and the first film, whereas in the peroral test the interval was 14 hours. It has been established, however, that there is no constant superiority of shadow at any one time between the limits of 14 and 17 hours, so that the unequal interval before filming need not be considered as unfair to one or the other test. Otherwise the procedure, once the drug was administered, and until the last film had been made, was identical for both groups. Suffice to say that each set of films was reviewed independently by one of us (E. P. P.) without any clinical facts of the case at hand, and a second comparison made.

Results. Three facts stand out as a result of the comparison; First, that the peroral test was inconclusive, in spite of careful technique, in one-third of the cases; second, that the observation of the dye shadow in the intestinal tract was an absolute necessity before the interpreter could make a report of a non-functioning gall bladder on the oral test; and third, that the reactions to the intravenous technique, while not alarming, were such as to necessitate great care in its administration.

In Tables 2 and 3 the results of the parallel series are summarized. One-fourth of the patients had normal cholecystograms by both methods, and in the majority of these the shadows were equally satisfactory for the interpreter. Both tests agreed in showing abnormal function in approximately one-third of the number, making the total of agreement 61 per cent.

Of the remaining 39 per cent the peroral method was 6 times more often inconclusive, for one reason or another. In 27 of the 34 doubtful peroral results, the fault lay with the test and not with the patient. Of the 32 instances (Table 2) where the gall bladder was found to function normally by the intravenous test after the peroral had led to an abnormal or unsatisfactory report, the clinical and

other laboratory data confirmed the intravenous in 25, or 73 per cent. Poor utilization of the dye, with insufficient shadow, and loss of dye due to reactions were, so far as could be determined, the main causes of the inconclusive oral tests. In 3 oral and a like number of the 5 inconclusive intravenous tests, gas in overlying bowel obscured the picture.

TABLE 2.—COMPARISON OF RESULTS.

Normal function by both tests	25
Abnormal function by both tests	36
Peroral inconclusive, intravenous normal function	32
Peroral: Abnormal function	15
Doubtful	12
Unsatisfactory	5
Intravenous inconclusive, oral normal	5
Peroral unsatisfactory, intravenous abnormal	2
Totals: Tests in agreement	61
Tests at variance	39

TABLE 3.—RELATIVE EFFICIENCY OF THE METHODS.

Interpretation of the films:	
Intravenous more satisfactory	46
Peroral and intravenous equally satisfactory	36
Peroral more satisfactory	18
Checked by operation	14
Abnormal or absent function both tests, confirmed	12
Both tests normal, calculi at operation	1
Peroral, no function, intravenous normal and confirmed	1
<i>Total Series Checked Against Clinical Findings and Final Diagnosis.</i>	
Intravenous test agrees	88
Peroral test agrees	63

The interpreter, as was to be expected, was more often satisfied with the density of the intravenous shadow, when he compared the two. In a considerable number, however, the shadows were of comparable clarity. For a small series, the results reported by others were duplicated, namely, that in the type of case which clinically demands operation, the two tests agree in positive results. The peroral test, however, more often disagreed with the completed clinical workup when the less obvious cases are included.

An added result of the attention paid to the interpretation of the peroral cholecystograms was the confirmation of our previous observations that without homogeneous dye in the intestinal tract a pathologic gall bladder could not be reported even though no sign of the viscus appeared on the films. Delario⁵ has recently called attention to the characteristic dye shadow in the gut when the drug has been absorbed and secreted by the liver.

From the standpoint of reactions the advantage rests distinctly with the peroral technique. The figures in Table 4 represent the number of individuals reacting, whose major symptom is recorded. A few had, for instance, headache along with chill and fever, the

latter only being listed. The peroral tests were followed by untoward effects 18 times, the intravenous 54 times, including the thromboses. None of the intravenous reactions were alarming, however. Only 2 of the ambulant patients, 1 with a cirrhotic liver, and the other with a highly unstable nervous system, reacted sufficiently to require overnight hospitalization. There were no delayed reactions of any seriousness and follow-up visits or letters from 60 of the 100 patients indicate that in these individuals at least, no late effects have occurred.

TABLE 4.—REACTIONS.

Peroral method:	Total (nausea, vomiting or diarrhea)	18
	Interfere with interpretation of films	5
Intravenous method:	Total	43
	Urticaria	27
	Chill and fever	6
	Vomiting	5
	Nausea, headache or back pain	5
Local thrombophlebitis at site of injection		11
Blood pressure readings before and after injection in 14 unselected cases:		
	Unchanged	7
	Drop of 5 points	2
	Drop of 5 to 15 points	3
	Drop of 25 points (hypertension)	2

At the beginning a few rather severe chills occurred following the intravenous injections, which we ascribed to the distilled water used for the solutions rather than to the dye. When freshly sterilized Sunbeam water was substituted, that complication was avoided. Urticaria of varying severity was by far the most common reaction, and in 5 instances small injections of adrenalin were needed to control the itching. In spite of the great dilution of the dye (from 150 to 300 cc. of normal saline were used in each case), the vein wall was in a few instances sufficiently irritated to set up a local thrombophlebitis. No great discomfort and no disability resulted from the phlebitis which at the maximum extended only 10 cm. up the arm.

Blood pressure readings before and after the injection were made in a consecutive unselected group which included 2 hypertension cases. The moderate drop in tension was, in our opinion, due more to the patient's relaxation and loss of apprehension during administration of the dye than to its direct action on the vascular or nervous system. The hypertensive patients showed no ill effects whatever. No other circulatory phenomena were observed in this series.

Comment. Peroral cholecystography is a diagnostic method of great usefulness in suspected gall bladder disease. One is led, nevertheless, in the light of the present results to urge again that the clinician consider it as an aid to diagnosis in conjunction with other data, and not as making the diagnosis. Our results emphasize the fact that the peroral test, inconclusive in a third of the series, must

not be accepted as final in doubtful cases. Under such circumstances, *i.e.*, where the interpretation does not agree with other diagnostic data or where there has been question regarding utilization of the full quota of dye, the intravenous test should be made. A second peroral test after a week's interval may be of service if the intravenous is not available.

In this comparison a corollary worth mentioning was the demonstration in 1 case of the effect of passive congestion of the liver on the value of the tests. A mildly congested liver led to "absent shadow" reports in an ambulant patient both by peroral and intravenous methods. With suitable rest and digitalis therapy, a repeat peroral test was made and perfectly normal gall bladder function reported. Nothing in the history or subsequent course of several months has led us to suspect gall bladder disease in this particular patient. A liver which cannot adequately secrete the dye will, it must be remembered, give the same cholecystographic result as a gall bladder which cannot receive or concentrate the dye.

Conclusions. The peroral cholecystogram with the present technique has certain inescapable disadvantages, indicated by the fact that one-third of the tests in the present series led to uncertainty in interpretations or disagreed with the assembled clinical and laboratory data. On the other hand, this method is free of the chief drawbacks of the more accurate intravenous technique, namely, difficulty in administration and untoward reactions. It is justified as the single test of gall bladder function, however, only if its limitations in the mild or early case are appreciated by the clinician.

The intravenous technique may not be used casually or haphazardly. Its reactions, however, are not such as to preclude its use for office or dispensary patients.

The procedure suggested is that the peroral test be used routinely, to be checked in case of doubt by the intravenous. The intravenous injections should be made by a member of the clinical staff, experienced in the technique, at a fixed station where proper equipment is concentrated.

NOTE.—We desire here to express our gratitude to Miss Ethel M. Showers for her very valuable technical assistance.

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THE PATHOGENESIS OF PERIGASTRIC ABSCESS COMPLICATING PEPTIC ULCER.

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EVER since the subject of gastroduodenal ulcer has been intensively studied, the view has been held that perigastric abscess complicating peptic ulcer is the result of slow gradual perforation of the gastroduodenal wall. Brunner,¹ in his classical report on perforated ulcer published in 1903 indicated the current surgical opinion regarding perigastric abscess* in the following introductory statement: "My exposition is limited to ulcers which perforate suddenly into the free abdominal cavity to the exclusion of those which perforate either slowly or in the walled-off space resulting from preformed adhesions. The clinical picture in the latter cases is an essentially different one involving, as a rule, a more chronic affection which leads to delimited peritonitic, mainly subphrenic abscesses, the surgical management of which consists for the most part in simple incision." Up to the present time the view expressed by Brunner has remained practically unmolested, although experience with peptic ulcer and its complications has increased enormously. Moynihan,² who is rightfully considered one of the greatest surgical authorities on digestive ulcer, shares essentially the same opinion as Brunner. Moynihan separates perforation of ulcer into three varieties, *viz.*, acute, subacute and chronic. Regarding the latter, he states, "In chronic perforation the ulcer has slowly eaten its way through the stomach coats, and a protective peritonitis has had time to develop at the base. The escape of the stomach contents is, therefore, merely local; barriers of lymph confine the fluid to a restricted area and a perigastric abscess forms."

The internist, who has a better opportunity than the surgeon of observing the ulcer patient from the very start shares the identical view with regard to the genesis of a complicating abscess. The most

* For the sake of convenience the term perigastric abscess is often used in connection with perforated peptic ulcer to apply to collections of pus not only in the immediate gastroduodenal region but also in more remote sites, particularly the subphrenic spaces. Wherever mentioned in this paper, perigastric abscess has the above broad connotation unless otherwise specified.

representative medical opinions can be obtained, perhaps, from the latest works on diseases of the stomach. Rehfuß,³ after concluding his discussion on acute perforation, introduces the subject of perigastric abscess with the following paragraph: "Less dramatic in its intensity, but nevertheless accompanied by considerable gravity, is the formation of a subacute perforation followed by abscess formation. These patients usually present a history of months or years of chronic indigestion of the ulcerous type, obviously becoming more acute and more persistent. Sooner or later they are completely incapacitated by their pain and there is unquestioned evidence of a slow perforation. This is followed not by general perforation, but either by localized abscess formation or by the formation of dense adhesions and a fistulous tract into one of the adjacent organs, more particularly the liver or the pancreas." In connection with the consideration of the pathologic anatomy of ulcer complications Crohn⁴ speaks of "cases in which the perforation is a slow process (chronic perforation) with resultant limiting adhesions or local abscess formation." Similar opinions are found in almost all medical and surgical texts, a dissenting view such as expressed by Walton⁵ being quite exceptional.

In our clinical work at the Cook County Hospital with ulcer and its complications we had the opportunity of following from the earliest stages 8 patients who presented the final picture of "chronic perforation with perigastric abscess." In all of the patients observed the symptoms of onset were almost unmistakably those of acute perforation. In fact, a movable gas bubble, which is practically pathognomonic of rupture into the free abdominal cavity (Vaughan and Singer)⁶ was demonstrated roentgenologically in 5. Operation was not performed at the time of admission in the 8 cases because permission was not granted or the attending surgeon was in doubt as to the diagnosis. Our experience in these few instances of abscess following acute perforation led us to question the accepted frequency of chronic perforation as a cause of intraabdominal suppuration. We therefore undertook to investigate the incidence of acute and chronic perforation in cases which proved ultimately to be instances of perigastric abscess complicating peptic ulcer.

Through the courtesy and coöperation of our colleagues on the attending and resident staffs we were able to study, within the past 4 years, 22 additional patients with perigastric abscess of ulcer origin. Five were observed shortly after the acute perforation and for one reason or another were not operated upon but were allowed to progress to abscess formation. The remaining 17, when first admitted, complained of vague abdominal symptoms which were subsequently proved to be due to localized abdominal suppuration of ulcer genesis. In approximately two-thirds of the cases entering the hospital during the abscess stage, no mention of antecedent acute pain was made in the history. In these cases a sub-

acute or chronic perforation was assumed. By pertinent questioning with particular reference to the occurrence of previous violent pain which the patient failed to mention or to associate with the present illness, we succeeded without difficulty in obtaining a classical description of a previous acute perforation from 16 of the 17 patients. In each of these 16 cases the moment of rupture could be definitely and precisely established by the history. In the 1 remaining case an intolerable, overwhelming pain suggestive of perforation was not elicited. Of 30 cases, therefore, of perigastric abscess of ulcer origin evidence of acute rupture was obtained in 29, leaving only 1 in which a chronic or silent perforation may be assumed.

The present belief that perigastric abscess generally follows chronic perforation is based upon an incomplete knowledge of the natural history of ruptured ulcer. It is generally assumed that ulcers which, perforating acutely, not closed surgically, remain patent indefinitely and usually lead to death. In a small percentage of cases, according to current belief, recovery may occur, but only after a stormy and prolonged convalescence. While it is true that a rapidly fatal illness occurs in a certain proportion of unoperated cases, the course and outcome is by no means a uniform one. In an equal or possibly greater proportion of cases the original perforation, instead of remaining patent, becomes spontaneously closed and ceases to discharge material into the peritoneal cavity (Singer).⁷ In such cases the postperforative course does not conform to the classical case with unlimited leakage, but varies with the amount and character of the escaped gastroduodenal content. In that group of cases where spontaneous closure occurs rather late and the quantity of material extravasated is relatively large the resultant peritonitis is likely to be a severe one. If the patient survives, the diffuse peritoneal inflammation, after producing stormy manifestations, becomes focal and one or more localized collections of pus are likely to remain. Subsequent absorption, spontaneous or surgical evacuation, or extension of the inflammation may occur. In a second group in which the perforation is sealed earlier and the amount of efflux is considerably less, the ensuing peritonitis is likely to be of only moderate intensity. The more or less diffuse peritoneal inflammation runs a short and relatively benign course, lasting usually several days. After this time, unless absorption is complete, signs of abscess generally appear. In a third group of acute perforations with spontaneous closure the leakage is only slight and trifling in amount and the symptoms of peritonitis are mainly local and transient. In these cases which correspond to the *formes frustes* type of Singer and Vaughan⁸ the postperforative symptoms are surprisingly mild and frequently disappear within less than 24 hours, although a residuum of infectious material may remain. Failure to recognize the fact that walling-off of a perigastric abscess occurs after acute rupture has taken place, explains in a great

measure perpetuation of the view of chronic perforation with slow leakage.

Another reason why the conception of chronic perforation prevails, is failure to inquire into the illness which generally antedates the symptoms referable to the perigastric abscess. Between the time of recovery from the immediate effects of the acute perforation and the development of the abscess there is frequently an intervening period during which the patient may feel comparatively well. If chronic perforation is assumed to exist and the history of onset is not volunteered the acute pain of perforation will be overlooked. Even in those cases where the extravasation is rather copious a noteworthy improvement may occur before symptoms and signs of abscess supervene. In Case 1, for instance, the patient, following a severe diffuse peritonitis, was restored to fair health and was ambulatory for a time before manifest symptoms of abscess appeared. In the cases with moderate escape of gastroduodenal content it is the rule to observe a decided improvement in the patient's condition before the abscess asserts itself clinically. After the peritonitis of onset has receded and the patient has felt comparatively well for a few days and perhaps ceased to remain confined, symptoms of abscess are likely to supervene and force the patient to return to bed. Here, as in the previous group, there may be a latent period of days, weeks or months following apparent recovery from the perforation before the abscess makes its presence felt. During this time the patient's health is likely to be somewhat impaired, although no local symptoms or signs are noted. In those cases with minimal leakage an abscess, if it occurs, manifests itself, as a rule, after the patient has to all appearances completely recovered from the perforation. The brief and tranquil illness immediately subsequent to the acute rupture is usually followed by a variable period of good health, during which time the patient is able to carry on his former occupation. When the abscess begins to evidence itself, the incident of the perforation and its immediate effects are no longer fresh in the mind of the patient and the two illnesses generally are not associated. It is necessary, in this group particularly, to obtain a minute-by-minute history if the onset of the acute, sudden, violent pain of perforation is to be elicited.

That chronic, silent perforation does occur cannot be denied. A localized phlegmonous gastritis at the base of an ulcer may extend to the peritoneum, as suggested by Payr,⁹ and lead to the insidious development of an intraperitoneal suppurative process. However, the presence of a phlegmon in association with a peptic ulcer is extremely rare. A second and more likely occurrence is that bacteria may, with relative silence traverse the thin, unruptured base of an ulcer as described by Guibal¹⁰ and von Bergmann.¹¹ Here, however, the escape of organisms is relatively slow and the peritoneum is well able to protect itself against invasions of this type in all but

the exceptional case. The development of a purulent peritonitis proceeding from an ulcer with an intact base can be considered a rare event. For practical purposes the pathogenesis of perigastric abscess complicating ulcer other than acute perforation can be disregarded.

A correct conception of the relationship of perforation of an ulcer to perigastric abscess is of both diagnostic and therapeutic importance. We consider the knowledge that intraabdominal abscess results from acute rather than chronic perforation necessary for the early recognition and intelligent treatment of many cases of perigastric abscess. For diagnostic purposes the concept of chronic perforation is valueless and often misleading. It assumes that the solution of continuity of the gastric or duodenal wall occurs so slowly and silently that the actual time of rupture cannot be determined. The earliest evidence of perforation, according to this view, is the presence of a clinically recognizable abscess. In other words, the diagnosis of an abscess is required before a perforation can be suspected. The notion of acute perforation here elaborated makes the diagnosis of perigastric abscess possible during its incipency. A history of sudden, violent pain having the well-known characteristics of a perforation, followed later by vague abdominal complaints and when sought for, a slight rise in temperature is sufficient to direct attention to the probable presence of a perigastric abscess. The value of the acute perforation doctrine in diagnosis and therapeutics is well exemplified in the appended case reports dealing with intraabdominal suppuration of ulcer origin.

Case Reports. CASE 1.—F. C., a man aged 55 years, entered the Cook County Hospital on June 14, 1929. The history obtained at that time and recorded on the chart was that 38 hours before admission the patient, while walking in the street, experienced an epigastric pain which increased rapidly in intensity and caused him to return home and take to bed. After 24 hours the pain began to diminish in intensity but did not subside completely. He vomited several times the day after onset following attempts at drinking. No bowel movement occurred since onset. No history of previous similar attacks or of any gastrointestinal symptoms other than constipation was elicited. The remaining history was essentially negative except for the presence of a chancre in 1899.

The physical examination disclosed a well-developed colored male, rather acutely ill. The temperature was 100° F., the pulse 64, and the respiratory rate 18. The blood pressure was 144 systolic and 68 diastolic. The physical observations consisted of the following: The pupils reacted normally to light and accommodation. The heart was irregular and the tones somewhat distant and weak. The abdomen was rigid, particularly in the right upper quadrant. Moderate tenderness corresponding to the extent of the rigidity was elicited. The liver dullness was not obliterated. The knee jerks were sluggish. In the urine a 4+ reaction for albumin was obtained and numerous casts were seen in the sediment. The white blood count was 10,550. The diagnostic considerations included a coronary occlusion or dissecting aortic aneurysm and an acute abdominal condition due to mesenteric embolism, ruptured ulcer or perforative appendicitis. Owing to the obscurity of the diagnosis the attending surgeons decided that operation was not indicated.



FIG. 1.—Case 2. Roentgenogram taken, March 13, 1930, 15 days after acute pain of ulcer perforation. Beneath the right diaphragmatic dome is a fluid level (subphrenic gas-containing abscess) indicated by arrow. The opacity at the base of the right chest is due to fluid.



FIG. 2.—Case 2. Appearance of film of March 15, 1930, taken 2 days after Fig. 1 and 17 days after perforation. The shadows produced by the subdiaphragmatic air (indicated by arrow) and the supradiaphragmatic fluid have decreased in size.

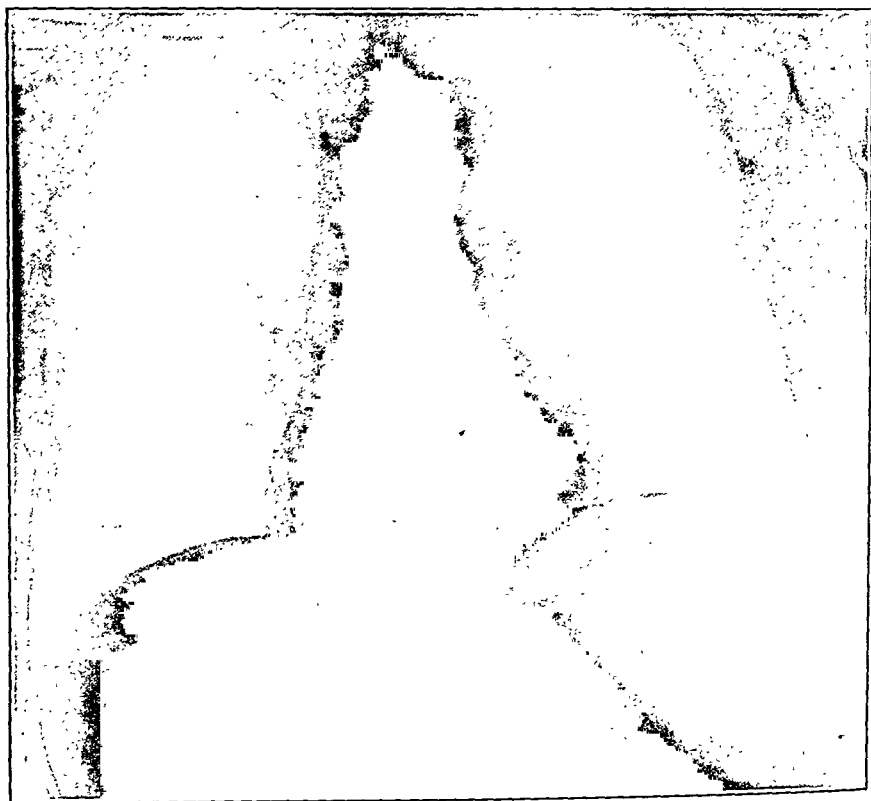


FIG. 3.—Case 2. Artificial pneumoperitoneum performed, April 28, 1930, resulting in the accumulation of air beneath the left dome. No air is seen to collect between the right leaf of the diaphragm and the dome of the liver indicating obliteration of the right subphrenic space.

The patient improved rapidly, and on June 16, 1929, 2 days after entrance, it was recorded the patient felt well and that the temperature did not rise above 99.4° F. Ten days after admission, a firm, smooth mass was palpated in the right subhepatic region. The thought of a kidney tumor as the cause of the symptoms suggested itself and cystoscopic examination was advised. Pyelography failed to show any abnormality of the right renal pelvis. The surgeons were unable to arrive at a satisfactory conclusion and transferred the patient to the medical service 2 weeks after admission for diagnostic study. While in the medical ward the subhepatic mass disappeared, the patient became afebrile and the pulse assumed a regular rhythm. Various types of examination were resorted to but none seemed to throw any light upon the origin of the patient's symptoms. He was discharged in apparently good health on August 3, 1929.

Two weeks later the patient was readmitted to the hospital on account of pain in the upper abdomen which appeared rather suddenly 5 days after he returned home. It was somewhat sharp at onset but gradually diminished to a mild pain which persisted. A few days after the onset of the pain the patient perceived an egg-sized, firm mass in the left upper quadrant which had progressively increased in size. The temperature, pulse and respiratory rates were normal. The contour of the abdomen was distorted by the prominence of a mass in the left hypochondrium which was the size of an orange, tender and slightly mobile with respiration. A tentative diagnosis of carcinoma of the transverse colon was made. A barium enema disclosed no abnormality of the colon.

At this juncture we had occasion to interview the patient regarding his past and present illness. By painstaking and persistent questioning we obtained the following significant history: For many years the patient has suffered from mild epigastric distress which he ascribed to constipation and which, when analyzed, had the characteristic rhythmic relation to meals and the seasonal periodicity of ulcer pain. During the 3 days preceding the onset of acute pain which occurred prior to his first entrance, the patient experienced an augmentation of his previous epigastric distress and suffered also from night pain and vomiting. On June 12, 1929, at about 7 P.M., following a day of considerable discomfort and almost complete abstinence from food on that account, the patient was suddenly seized within a half block of his house by a severe epigastric pain. He stooped forward, and with his arms crossed over his abdomen he succeeded, after much effort, in arriving home. By this time the pain had reached its acme and was exceedingly violent and acute. The patient flung himself onto his bed and writhed about in an attempt to find a comfortable position. A physician who was summoned arrived within a hour of onset and administered a hypodermic which rendered the pain less intense but did not entirely alleviate the patient's suffering. A second hypodermic was required a little later, and after 24 hours the pain moderated sufficiently to permit the patient to rest.

After obtaining the above history and reflecting on the physical signs noted at the time of the initial admission we inferred that the patient had probably suffered an acute perforation of a chronic ulcer. A review of the history indicated that the symptoms and signs recorded during his first period of hospitalization were quite characteristic of the postperforative stage of a ruptured ulcer which had been spontaneously sealed. The subhepatic mass which appeared and later disappeared we assumed to be a collection of gastroduodenal content and purulent exudate which was absorbed or spontaneously evacuated. After reaching the conclusion that a

previous rupture had occurred, it was a simple matter to associate the tender mass which recently appeared with the antecedent history. A diagnosis of perigastric abscess was therefore made and operation advised. Our colleagues were still somewhat hesitant in accepting our opinion, and on August 30, 1929, a Roentgen ray examination of the stomach was ordered and the following report rendered: "The right diaphragm is abnormally high and relatively fixed. There is a deformity of the bulb characteristic of ulcer." On September 3, 1929, approximately 12 weeks after perforation, laparotomy was performed and a perigastric abscess was found and drained. The patient made an uneventful recovery and was discharged September 19, 1929. Up to the present date he has had no further difficulty, except at times when he becomes lax with his diet and medication.

CASE 2.—M. M., a well-preserved man, aged 66 years, admitted to the medical service on March 11, 1930, complained of belching and epigastric pain of 2 weeks' duration. In the hospital record his history, as obtained by the junior intern, reads as follows: "The patient felt perfectly well until 2 weeks ago, when he suffered from severe cramp-like abdominal pain which lasted for a day or so and then gradually subsided. Vomiting, which occurred for the first time 2 days after the onset of pain, was repeated 2 or 3 times daily since, but ceased 24 hours preceding admission. There has been no relationship of the vomiting to the quality or quantity of food eaten. During the first few days of his illness hiccough was a prominent symptom but has now completely disappeared. For the past two years there has been dyspnea on exertion, which became aggravated recently and associated with cough and expectoration especially upon change of position."

The temperature upon entrance was 99.2° F.; the pulse rate, 76, and the respiratory rate, 20. The blood pressure was 120 systolic and 72 diastolic. The physical observations were those of an insufficiency of the mitral valve, effusion in the right chest, a tender, palpable liver and a slight edema of the ankles. A diagnosis of right pleurisy with effusion probably tuberculous and an independent myofibrosis with a relative mitral insufficiency was made. Later it was attempted to explain the entire picture on the basis of a decompensated heart until thoracentesis was resorted to and yielded 400 cc. of a clear fluid having the characteristics of an exudate. Vomiting recurred 2 or 3 times daily while the patient was under surveillance. One of the attending physicians being apprized of the emesis succeeded in obtaining the additional history of postprandial distress and diagnosed a peptic ulcer in addition to a right pleural effusion. A relationship between the two was considered but thought unlikely. An Ewald test meal on March 12, 1930, yielded 250 cc. with 67 degrees free and 85 degrees combined acidity.

At this point in the course of observation we had the opportunity of questioning and examining the patient. We elicited the story that for 15 years he had suffered periodically from epigastric distress which was typical of peptic ulcer. He had consulted no physician, as he could always obtain practically instantaneous relief from baking soda, which he used in large amounts. Prior to the onset of acute pain he noted no unusual deviation from his chronic ulcer distress and no symptoms which might have been considered prodromes of a perforation. On February 26, 1930, at 6 P.M., while reclining on account of languor, the patient was suddenly seized by violent abdominal pain which began on the right side but within a few minutes became generalized. The patient broke out in a cold sweat and began to writhe about in agony. His abdomen, which he attempted to

protect with his hands, became as "hard as iron." He called to his wife and implored her between gasps to telephone for a physician immediately. During the 30 minutes that elapsed between the time the physician was summoned and his arrival the patient suffered from intolerable pain which he believed he could not have endured much longer. A hypodermic was immediately administered, following which the patient's suffering was somewhat relieved. The pain gradually diminished in intensity and by the following day it was relatively mild. Hiccough was first noted the day after onset and subsided readily to recur for short periods at intervals of a day or so. Four days after onset the patient first began to vomit. Shortly before entrance both the pain and emesis completely subsided. The reason the patient came to the hospital at this time was mainly on account of debility and shortness of breath.

Based upon the history which indicated a recent perforation with diaphragmatic irritation (hiccoughing), the evidence of fluid in the right chest, the depressed liver and a subfebrile temperature, the diagnosis of subphrenic abscess with pleural extension was made. Our diagnosis was questioned until Roentgen ray examination (Fig. 1) undertaken on March 13, 1930, showed a high right diaphragm above which was radiographic evidence of fluid and below which was fluid and air. A barium meal disclosed the presence of a prepyloric deformity which caused 90 per cent retention at the end of 6 hours. The evidence of an ulcer and of a subphrenic abscess was therefore conclusive. The history pointed almost unmistakably to a direct relationship between the two affections. On account of the spontaneous improvement operation was not urged. A modified Sippy treatment for ulcer including bed rest was instituted. The temperature gradually dropped, the vomiting ceased and the abdominal pain subsided. Subsequent Roentgen ray examinations (Fig. 2) showed a progressive decrease in the supra- and infradiaphragmatic shadows, both of which disappeared by April 4, 1930. The diaphragm on this day showed a normal mobility, the prepyloric deformity persisted, but no retention of the 6-hour barium meal occurred. The patient left the hospital April 11, 1930, feeling quite well. He returned to the follow-up clinic complaining of shortness of breath and was advised to reënter the hospital for cardiac management. On rest and digitalis his heart symptoms vanished. Before final discharge of the patient it was decided to investigate the relationship between the superior surface of the liver and the right dome of the diaphragm. For the determination of the presence of subphrenic adhesions, artificial pneumoperitoneum was resorted to (Fig. 3). In no position was it possible to cause air to enter the right subphrenic space, which was assumed, therefore, to be obliterated as a result of organization of the previous exudate.

Summary and Conclusions. 1. In a series of 30 cases of perigastric (including subphrenic) abscess of ulcer origin, convincing evidence of a previous acute perforation into the free abdominal cavity was obtained in 29.

2. The formation of adhesions which are found about a perigastric abscess generally follows rather than precedes perforation.

3. Between the time of recovery from the acute symptoms of perforation and the time of onset of manifestations of a perigastric abscess a period of fair health frequently intervenes. It is on this account that a patient often fails to associate the two illnesses.

4. Unless a previous acute perforation is suspected and a minute-by-minute history of the initial symptoms obtained, the antecedent occurrence of a sudden, violent abdominal pain is often not elicited.

5. In most instances a perigastric abscess of ulcer origin represents a neglected opportunity on the part of the patient, but perhaps more frequently on the part of the physician.

6. Early recognition of perforated peptic ulcer, especially the type with mild postperforative symptoms (*forme fruste*), together with timely operation will eliminate the greater number of perigastric abscesses.

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INSULIN AND APPETITE. I. A METHOD FOR INCREASING WEIGHT IN THIN PATIENTS.

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It is not generally appreciated that insulin plays an important rôle in the hunger-producing mechanism. As far back as 1924 Harris described 3 cases of hyperinsulinism in which the patients

suffered insatiable hunger, and he suggested that insulin was closely associated with the hunger mechanism. Bulatao and Carlson have injected insulin in normal fasting dogs and obtained increased gastric motility, an activity which was readily inhibited by injecting dextrose. A similar experiment was performed on human subjects by Quigley, Johnson and Solomon. They injected 12 to 20 units subcutaneously in normal fasting men and demonstrated that marked sensations of hunger accompanied the increased gastric motility. These phenomena, too, could be readily inhibited by introducing dextrose into the duodenum.

This simple yet effective method of increasing the appetite is seldom employed clinically. In the few case reports concerned with this treatment, the results have been gratifying in large measure. Falta, in 1925, reported the results in 3 abnormally thin patients to whom he had administered insulin as a stimulant to the appetite. Two had suffered with a chronic infection of the throat, while the third was thin but otherwise normal. In each case the state of nutrition was poor and the resistance to disease inadequate. The appetite was small and the caloric intake was low. Falta employed injections of 10 to 15 units of insulin every 3 hours and furnished large amounts of food at all times. The patients quickly developed wellnigh insatiable appetites, consumed greatly increased quantities of food and gained from 10 to 20 pounds in 20 to 40 days. In one case, the appetite was increased so markedly as to closely resemble bulimia.

The number of thin patients who are otherwise normal is considerable. Out of the last 100 private patients who consulted one of us, 4 were in this category. Add to this number the patients convalescing from prolonged illnesses, and the large population in state institutions who stop eating because of mental depression and anxiety states, and the total becomes even more considerable. The appetite in most of these patients is not large and in some cases excessively small, so that the caloric intake is insufficient to maintain the nutritional state adequately. Most of them have resorted to the usual tonics and stomach bitters without any benefit and have finally accepted their reduced physical proportions and poor cosmetic effect with hopelessness and resignation. In this type of patient insulin quickly converts a meager appetite into a large one and the food intake is increased proportionately.

The Method. The treatment is begun by administering 3 units of insulin subcutaneously every 3 hours. In order to avoid an insulin reaction, patients are urged to eat liberally $\frac{1}{2}$ hour to $\frac{3}{4}$ of an hour after the injection. The dose of insulin is gradually increased until 10 units or even larger doses are injected every 3 hours. The patients are further acquainted with the nature of an insulin reaction and are urged at all times to have available carbohydrates in case an urgent need for it arises. The following cases are striking in their

improvement and illustrate clearly the case of the method and the absence of untoward incidents during the treatment:

Case Reports.—**CASE 1.** M. T., female, unmarried, aged 33 years, housekeeper, F. H. and P. H. not significant, has always been highstrung and worrisome. Six months ago an episode in the home greatly upset her. Since then though the facts and situation have been almost forgotten, her appetite has grown meager and her weight dropped steadily from 130 pounds to 100 pounds. She could not eat much, was quickly satisfied and felt full after ingesting a small meal. She has grown sensitive about her looks and has therefore avoided her friends. Furthermore, she was fearful about the possibility of having tuberculosis. Her menstrual history was normal. The physical examination revealed nothing of note except that she was thin, weighing only 100 pounds though 5 feet 5½ inches tall. For 3 weeks she was given relaxing packs and tonics, a complete rest from home duties and a change of environment. Three weeks later she weighed 102½ pounds. She was then placed on an insulin régime. On the third day, the patient was awakened during the night suffering from weakness and sweating and all signs of an insulin reaction, and occasionally a similar weak feeling was experienced just before the evening meal. The gain in weight was very rapid. In 3 days she weighed 105½ pounds; in 7 days, 108½ pounds; in 14 days, 115 pounds; in 21 days, 119½ pounds; in 28 days, 125 pounds. Her cheeks became rounded and her figure improved. She regained confidence in herself and returned to her former social life. Three months later her weight was unchanged and she seemed normal in every respect.

CASE 2.—H. Q., female, aged 24 years, height 5 feet 7½ inches, weight 108½ pounds, has always felt well. Her immediate relatives are living and well nourished. Four years ago she had acne of the face which left it somewhat scarred, since then her weight has gradually fallen from 130 pounds to 108½ pounds. Her appetite seemed good and she claimed to eat well, but her weight remained consistently low. She was of a nervous temperament, worrisome and always accepted other peoples' burdens. The treatment was started with 5 units every 3 hours. After the first injection there was created great relish, and for the first time she really enjoyed her meals. The food intake rose rapidly and 3 days later the weight was 110½ pounds. At this time the insulin was raised to 10 units every 3 hours. Three days after the dose was increased her weight was 112½ pounds, 5 days later 118½ pounds, so that in 12 days the weight had increased 10 pounds. The following is a characteristic day's food intake for this patient:

Breakfast: 2 oranges, 2 slices of buttered-toast, 1 egg and a glass of milk.

At 10.30 A.M.: Two frosted cupcakes and a glass of milk.

At 1.00 P.M.: A large salmon salad, a whole heart of lettuce, 2 heaping tablespoons of mayonnaise, 1 egg, 2 rolls, 2 cubes of butter, 2 slices tomatoes and 2 olives, a Bisque Tortoni and a glass of milk.

At 3.00 P.M.: A Hershey chocolate bar.

At 6.00 P.M.: Six oysters, a plate of tomato soup, a quarter of a chicken, 2 baked potatoes with a tablespoon of butter, a helping of spinach, 5 tablespoons of fruit jello, 3 slices of bread and 3 tablespoons of butter, 6 chocolate cookies and a glass of milk.

It is not difficult to appreciate why there was a rapid gain in weight following the intake of such a quantity of food. The insulin was then discontinued and the weight remained at 118½ pounds for a month.

CASE 3.—A. S., female, aged 20 years, married 1 year, complains chiefly of nervousness, weakness, loss of appetite, and loss of weight during several months. At this time she consulted a physician for pain and stiffness in her knees. She was told she had rheumatism and warned of possible heart disease to follow. Although her pains were fleeting, she continued to brood

and worry because of her heart, lost appetite and began to lose weight. Examination revealed no abnormalities; her height was 5 feet 6 inches; weight, 112½ pounds. This patient was started with 5 units of insulin given every 3 hours for 18 days, and then experienced for the first time real pleasure in her eating. There were several instances during the treatment when mild insulin reactions occurred. These, however, were finally eliminated by increasing the food following each injection. The weight rose to 115½ pounds in 3 days. In 6 days, it was 116½ pounds; in 8 days, 117½ pounds; in 10 days, 118½ pounds; in 12 days, 120¼ pounds; in 18 days, it had only risen to 121 pounds. At this point the insulin was raised to 7 units every 3 hours. The weight did not improve but instead moderate insulin reactions of weakness, sweating and faintness occurred after the afternoon dose and also at night. Accordingly the dose was reduced to 5 units and the food intake was increased after the afternoon and night dose. Five days after this change the weight was 125 pounds. The insulin was then discontinued, but the weight has remained at 125 pounds for 1 month.

CASE 4.—T. N., female, aged 26 years; height, 5 feet 7½ inches; weight, 110 pounds. Apparently well and in good health but thin and desiring to improve her weight and thereby her appearance. She was endowed with but a frail appetite which was quickly satisfied. She was started on 3 units every 3 hours, November 10, 1930. At this time the weight was 112 pounds. On the 18th, the weight was 118.6 pounds, and the dose was increased to 10 units every 3 hours. The weight steadily rose until December 9, when it was 126.6 pounds. At this time insulin was discontinued because of an intercurrent gripe. December 15, the weight had fallen to 122 pounds and insulin was resumed to 10 units every 3 hours. On the 17th, the weight rose to 124 pounds, and on the 19th it was 125 pounds. The insulin was then discontinued and the weight 6 months later was 121 pounds although she had just recovered from an intercurrent illness of 2 weeks' standing.

Discussion. The rapidity with which the appetite is restored and the quantity of food intake is increased is thus well illustrated in Cases 1 and 3. The first patient gained 22½ pounds in 28 days, the second gained 10 pounds in 12 days, the third gained 12½ pounds in 23 days and the fourth gained 15 pounds in 39 days. The untoward insulin reactions were surprisingly small when one considers that 45 to 65 units of insulin were administered daily to normal persons.

The question has been raised as to whether the rapid weight increase is due to water retention. This is hardly likely as the caloric intake was doubled and tripled during the treatment. Furthermore, the gain in weight remained for the most part after the insulin was stopped. Temporary water storage under insulin treatment should be rapidly eliminated when this hormone is discontinued, and the weight should revert quickly to the former level. This did not occur in these patients. Falta tested this possibility further on his patients by administering large doses of diuretics but failed to produce increased water elimination and loss of weight. He also concludes that water storage is not an appreciable factor in the rapid improvement in weight under insulin administration.

On the other hand, there is sufficient evidence that insulin does promote fat deposition. It has been known for years that rabbits employed for the assay of insulin gain weight rapidly the first few

weeks. It is also well known that depancreatized dogs when treated with proper amounts of insulin and diet can be made to gain weight rapidly. It is of course well known that most diabetic patients who are on a liberal diet with sufficient amounts of insulin gain weight rapidly. The rapid gain in weight of the cases above described, therefore, are more likely due to fat deposition. Furthermore, it has been shown that insulin causes a decrease in blood fat, apparently due to storage.⁷

It is remarkable to compare the amounts of food taken before treatment with what was ingested during the treatment. A. S. was satisfied with tea and one-half a slice of toast for breakfast, but after 10 units of insulin took a glass of orange juice, a bowl of oatmeal with sugar and cream, 2 rolls and butter, 2 eggs, and a glass of milk. All this she ate with real pleasure and gusto. Ingestion of such an amount of food before she took insulin would have been impossible and might even have nauseated her. It seems as if the capacity of the stomach was considerably increased after the insulin injections. It is quite probable that the size of the stomach plays an important rôle in determining the amount of food which can be taken with pleasure. It is well known that after chronic starvation, one can take but very small amounts of food and that only after several days does the capacity of the stomach become normal.

The physiology which underlies the pleasure of eating is still obscure. The patients of this series had clearly lost the zest obtained from food, before treatment was begun. Eating was more a habit than a pleasure, something to be despatched with rapidity as a necessity of life. Following the administration of insulin, however, a feeling of pleasure appeared and as the dose was increased so was the joy of eating. Patient 3, who was nauseated by the sight of food before treatment, developed a ravenous appetite, and following insulin administration ingested large quantities of food with relish. Thus, insulin not only creates hunger, but also generates the pleasure which is associated with its satisfaction.

It has long been known that patients subjected to worry and anxiety quickly lose the appetite and grow thin. That the mind may mediate these effects through the insulin mechanism, gains support from recent work. Beattie, Brow and Long (1930) have traced anatomic pathways from the hypothalamus to the sympathetic fibers in the cord and have thus established a direct connection between the brain and the sympathetic nervous system. Stimulation of this region of the brain will cause a rise in blood pressure and a discharge of adrenalin from the adrenal glands. It is now known that adrenalin tends to inhibit insulin activity^{3, 4} while the sympathetic fibers paralyze gastrointestinal motility. It is also conceivable that the sympathetic nerves may cause an inhibition of insulin formation by a direct action on the pancreatic cells. It

is therefore not difficult to understand how emotional states can, through the sympathetic nervous system, interfere with the insulin mechanism and so diminish the appetite.

Summary and Conclusions. 1. Four patients are reported who gained weight rapidly following the administration of insulin. As a result of the treatment, there was a great increase in the appetite, probably a considerable enlargement of the stomach capacity and the generation of great pleasure associated with eating.

2. The gain in weight is not due to water retention, but rather to actual tissue accretion.

3. The relation of mental states to anorexia is considered, and their influence upon the insulin mechanism is traced.

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METABOLIC CHANGES AND TREATMENT OF OBESITY.*

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THE attention of every physician is directed sooner or later to the question of obesity; not only because of the desire of some patients to reduce for esthetic reasons, but because in obesity there are real inherent dangers. The susceptibility of the obese person to infectious disease, especially pneumonia, to diabetes and to the degenerative diseases of heart and bloodvessels is sufficient ground for our interest in the subject. It is my object at present to discuss some phases of obesity, which although not new, yet are of sufficient importance to be worthy of review, and to describe the rôle that dehydration may play in the therapy of some forms of obesity.

Obesity is usually classified as that of exogenous or of endogenous character. By exogenous is implied that the person becomes obese because he eats too much or exercises too little; in other words the principle of conservation of energy is operative in this type of obesity. DuBois¹ aptly said, "We do not yet know why certain

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individuals grow fat. Perhaps it would be more accurate to say that we do not know why all the individuals in this overnourished community do not grow fat." It is apparent then, and it is generally admitted by students of obesity that there are some persons in whom there are some additional factors besides the excess of food or insufficient muscular exercise which would tend to account for the tendency to become obese. We refer to the so-called endogenous type of obesity. In practice it is frequently difficult to know where exogenous obesity ends and endogenous begins. In the person who has a tendency to become obese there must be some disturbance of the mechanism which enables another person to burn an excess of food and to retain his stationary weight.

Some of the obese patients have an excessive desire for food, and by attempting to reduce their caloric intake they may suffer from weakness, fatigue, headache and dizziness, and nervousness and yet fail to lose weight. It is this type of obesity that constitutes the problem in the management of the disease.

In concerning ourselves with obesity we must consider the total metabolism of the individual, that is, his or her basal metabolism, the effect of exercise on oxygen consumption, the stimulation in metabolism that follows the ingestion of food, that is the specific dynamic action of food. Water and salt metabolism are also of importance and in some patients appear to play a prime rôle in the gain or the loss of weight.

Basal Metabolism. Out of 21 patients who were under our observation within the last 12 months, only 2 patients had a perceptibly minus basal metabolic rate. One patient (No. 1) was a boy, aged 13 years, who had dystrophia adiposogenitalis and whose basal rate was minus 30; the other was a woman, aged 47 years (No. 20) who had a thyroövarian obesity, whose basal rate varied between minus 20 and minus 30, average minus 25, on two different occasions. The third patient (No. 12) in whom the basal rate markedly deviated from the normal and whom we shall discuss again later, was that of a man, aged 38 years, with cerebral obesity; he had a basal rate of plus 30. Patient No. 3 had a basal of plus 47. This patient developed thyrotoxicosis after she commenced to put on weight. All the other patients showed basal metabolic rates within the range of normality. This is in accordance with the experience of most clinics.^{2,3} The conception of van Noorden that mild forms of hypothyroidism lead to obesity is, therefore, not borne out by facts.⁴

I recently studied a group of patients with hypothyroidism, all of whom had a minus basal metabolic rate.⁵ Four out of 7 of these patients were underweight rather than overweight.

Different individuals respond variously to thyroid gland administration. According to Falta⁶ the administration of thyroxin in some persons is followed by symptoms of thyrotoxicosis; on the other

hand the same amount of thyroxin in other persons remains ineffective. We often observe a similar occurrence in obese persons.

TABLE 1.—BASAL METABOLISM IN OBESITY.

Name	Sex.	Age, years.	Weight, pounds.	Height, inches.	Basal metabolic rate.
J. K.	M	13	199	60	-30
F. G.	F	16	131	63	-13
H. S.	F	17	158	65 $\frac{3}{4}$	+47
R. B.	F	17	159	63	-9
M. G.	F	23	212	67	-7
M. S.	F	25	235	61	+2
V. M.	F	26	182	64	+5
R. R.	F	26	189	63 $\frac{1}{4}$	-17
N. N.	M	26	193	65	-2
H. C.	M	27	282	76	-10
A. C.	F	32	290	62 $\frac{1}{2}$	+7
T. B.	M	38	290	67	+30
J. S.	M	38	172	66	+4
N. S.	F	38	155	58	-12
C. W.	M	38	237	70	+2
M. H.	F	41	204	61	-15
J. B.	F	42	250	67	+7
I. G.	M	42	332	64	-5
C. R.	F	42	269	61	-9
J. R.	F	47	170	66 $\frac{1}{2}$	-25
N. T.	F	53	190 $\frac{1}{2}$	59	-2

One-half grain of desiccated thyroid gland three times a day was given to an obese patient; within 10 days she developed tachycardia, nervousness and an increased sense of body heat without having lost any perceptible weight. On the other hand I have at the present time under my care a patient who has been taking desiccated thyroid for a period of 2 years, commencing with 2 gr. daily and bringing it up to 10 gr. daily for 8 months, without any evidence of thyroid intoxication and without loss of weight. Then again there are patients who lose weight rather rapidly under small doses of thyroid. In this connection the work of Enderlen and Bohnenkamp⁷ as mentioned by Falta is of interest. They have shown that dogs with resected sympathetic nerve remain refractory to thyroid administration, while the same dose of thyroxin produces extreme emaciation and death in the control animals. Clinically it is known that patients who suffer from certain diseases of the central nervous system, such as epilepsy and syphilis of the brain, are resistant to thyroid therapy.

One must conclude, therefore, that thyroid hypofunction and consequently a low basal rate is of no great moment in the pathogenesis of obesity.

The Specific Dynamic Action of Food. One would expect in obesity a low specific dynamic action of food. Some early workers like Plaut,⁸ Rolly⁹ and Liebesny¹⁰ had demonstrated a diminished specific action in obesity. However, Lauter,¹¹ Bauer¹² and others have found figures that do not materially differ from the normal. Wang,

Strouse and Saunders¹³ found that carbohydrate and fat has very little effect on the specific dynamic action; however, protein gives the greatest depression in the curve. Strang and McClugage¹⁴ have recently found no great difference in the heat of reaction to food in either mild or severe grades of obesity as compared with normal persons; they deny an abnormality in specific dynamic action any rôle whatsoever in the initiation of obese states. Spencer and McClelan, using the Sage calorimeter, have obtained normal curves for the specific dynamic action in obese men and women.¹⁵

I have studied the specific dynamic action of food in 7 obese patients.

TABLE 2.—EFFECT OF INGESTION OF A MIXED MEAL ON HEAT PRODUCTION.

Name.	Age, years.	Weight, lbs.	Height, inches.	Basal rate.	Metabolic rate.		Per cent difference from basal of patient.	
					45 min. after meal.	90 min. after meal.	45 min. after meal.	90 min. after meal.
J. K. . . .	13	199	60	-30	-30	-30	0	0
R. B. . . .	17	159	63	- 9	- 2	+ 5	7(+)	14(+)
T. B. . . .	38	290	67	+30	+20	+20	8(-)	8(-)
N. S. . . .	38	155	58	-12	-17	-10	6(-)	3(+)
C. W. . . .	38	237	70	+ 2	+ 5	+ 8	3(+)	7(+)
M. H. . . .	41	204	61	-15	+17	+25	38(+)	48(+)
L. G. . . .	42	332	64	- 5	+ 5	+ 2	10(+)	7(+)

The meal consisted of 100 gm. of meat, 200 cc. of bouillon, 30 gm. of butter, 100 gm. of bread and 3 gm. of salt. The readings were taken before the meal, 45 minutes and 1½ hours after the meal respectively. We obtained figures not markedly different from normal persons, with two exceptions: in one case of dystrophia adiposogenitalis, there was a total absence of specific dynamic action; in another case of thyroövarian obesity, the specific dynamic action was considerably increased over the basal rate. It is rather interesting to note that this patient was susceptible to thyroid therapy. One-half grain of desiccated thyroid gland three times a day for 10 days produced marked symptoms of thyrotoxicosis. In evaluating the specific dynamic action we must bear in mind that even in normal individuals it may vary from minus 1 per cent to plus 31 per cent.¹⁶ According to Pollitzer and Stoltz¹⁷ 25 per cent of normal individuals may show a diminished or complete absence of specific dynamic action.

Then again there are some patients who are extremely thin due to hypophyseal disturbance and also patients with diseased autonomic nervous system, such as Raynaud's disease or scleroderma, who also show low specific action of food. According to Plaut¹⁸ the specific dynamic action is under the influence of the anterior pituitary lobe. It is then apparent that the specific dynamic action is of no great practical moment in obesity.

The effect of muscular work on oxygen consumption in obesity

does not vary greatly from the normal. During heavy work the obese may consume more oxygen than a normal individual. Credit is due to Bernhardt¹⁹ for pointing out that after light muscular work, 20 minutes to 1 to 2 hours, the obese may show "negative phases," *i. e.*, consume less oxygen. Such negative phases may occur during the day in obese people, while normal people do not show negative phases. The occurrence of the negative phases in obesity does not, however, explain the origin of obesity. It may be of value in estimating the 24-hour "basal" caloric requirement for the obese. If one estimates all the positive phases of metabolism on the one hand, and on the other hand all the negative phases during the 24 hours, the sum total of heat production may be smaller than indicated by the basal rate.

Water and Salt Retention. Gamble, Ross and Tisdall²⁰ have demonstrated certain facts regarding water metabolism. According to them the total of chemical bases is important in maintaining the structural integrity of body fluid. They computed the water weight lost during fasting in terms of fixed bases and thus were able to determine the amount of water lost from cellular content and intracellular storage. Figures in one of their cases show that 62 per cent of loss of body weight was due to loss of water. Loss of body water during the 15-day fast of epileptic child A. G., studied by Gamble, Ross and Tisdall:

Intracellular water loss:		cc.
Due to destruction of protoplasm		1620
Due to reduction of cell volume		470
		<hr/>
		2090
Extracellular water loss		320
		<hr/>
Total loss of body water		2410
Loss of body weight	3920 gm.	
Body weight loss due to water	62 per cent	

From metabolic studies in starvation it is known that not more than 400 to 500 gm. of solids may be lost in 24 hours, yet losses averaging twice that much are not uncommonly seen in the clinic.²¹ It is clear that the great bulk of this must be water.

There are some obese patients in whom there is an unsuspected fluid and salt retention. Such patients when strictly dieted may actually be "undernourished," yet they suffer no loss of weight because of water storage. Van Noorden in 1910²² has already warned about the importance of water and salt restriction in the treatment of obesity. Zondek²³ designated such patients as of the "salt water obesity type."

Bauer²⁴ speaks of them as cases of "hydrolipomatosis." An accurate account of the water exchange in the obese has recently been furnished by Newburgh and his associates.²⁵ They have shown that their obese patients, when losing body tissues on strict metabolic regimen, held or even gained weight due to water retention.

We have selected a small group of 7 patients who responded poorly to the usual dietary treatment of obesity. To demonstrate the possible water retention in these patients methods were employed that could be carried out in an outpatient clinic, private office, or in a general hospital that is not especially equipped for

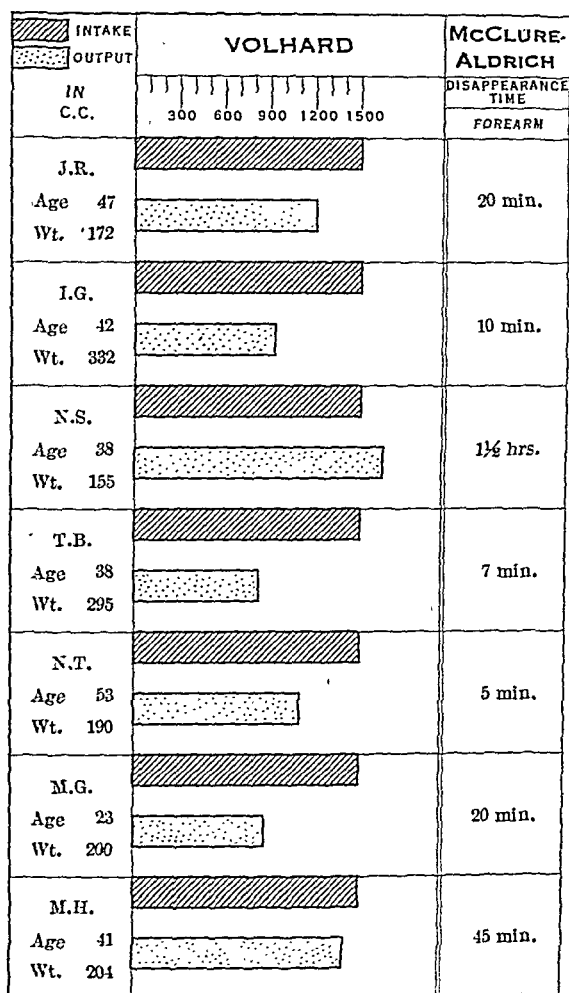


FIG. 1.—Volhard water test and McClure-Aldrich's intradermal salt solution test in 7 cases of obesity.

organized metabolic work. It is apparent that studies on water metabolism as recently described by Sunderman and Austin,²⁶ and Newburgh and his associates²⁷ could not possibly be undertaken on the material at hand.

The test for water retention was that of Volhard. In 5 out of the 7 patients there was a definite diminution in the urinary output

in the 4-hour period, the average patient showing a retention of 520 cc.

McClure and Aldrich²⁸ have shown that by injecting 0.2 cc. of 0.8 per cent salt solution intracutaneously into the flexor surface of the forearm and the inner surface of the calf muscle, a wheal appears which in normal persons remains an hour or longer. They

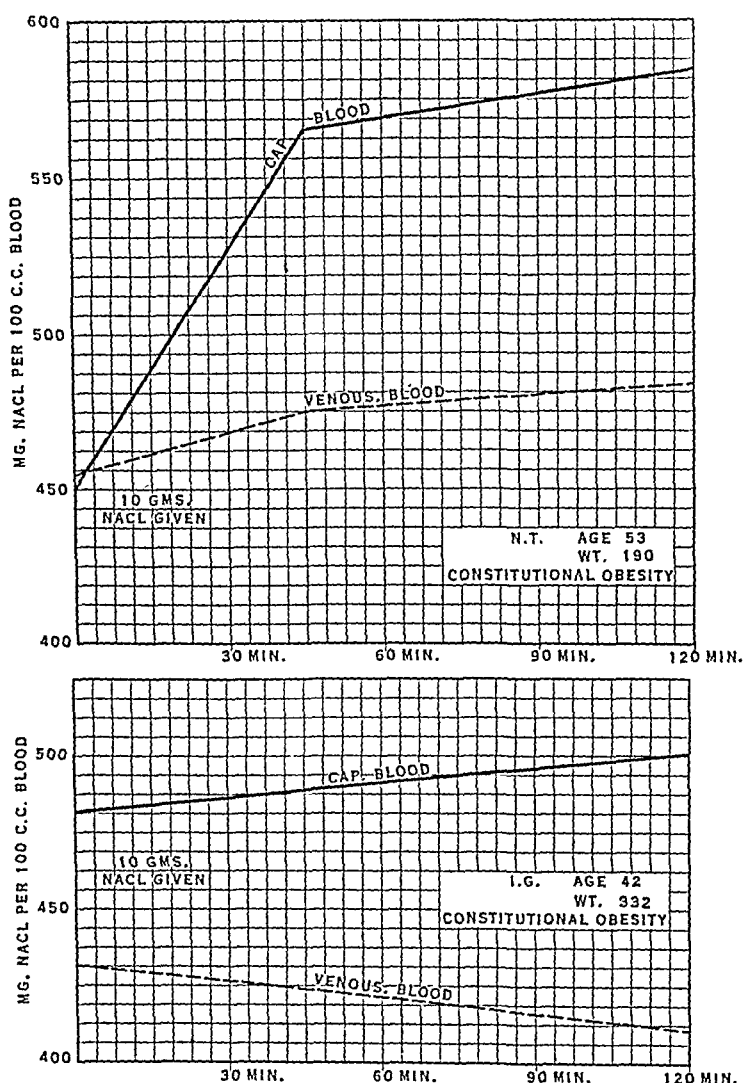


FIG. 2.—Sodium chlorid metabolism in 2 patients with obesity.

found that in renal edema the wheal disappears in a much shorter time. In our obese patients who tended to retain water the wheal disappeared in from 5 to 20 minutes after the salt solution injection.²⁹

In 5 patients we studied the NaCl of the venous and of the capillary blood after the administration of 10 gm. of NaCl by mouth. Before the salt was given, the NaCl of the venous and capillary bloods were about the same.

After the ingestion of NaCl the patients behaved differently. Two of them showed a distinct difference, the venous blood containing 100 mg. and 90 mg. respectively less than the capillary blood, 2 hours after ingestion of NaCl.

In 1 patient the difference between the venous and capillary blood chlorid was not marked, and in 1 patient the capillary blood at the second hour was not determined, although the NaCl of the venous blood increased 40 mg. more than at the beginning of the test. Patient Mr. T. B. showed a constant concentration of venous NaCl (300 mg.). At the end of 2 hours the capillary NaCl rose to 375 mg., while the venous NaCl remained at the same level as before the administration of NaCl.

TABLE 3.—SODIUM CHLORID METABOLISM IN OBESITY.

Name.	Age, years.	Weight, pounds.	Capillary blood, mg. per 100 cc.	Venous blood, mg. per 100 cc.	Diagnosis.
T. B.	38	291	350	300	Cerebral obesity.
45 min. after ingestion of 10 gm. of NaCl	330	300	
120 min. after	375	300	
Mrs. T.	53	190	450	454	Constitutional obesity.
45 min. after ingestion of 10 gm. of NaCl	564	474	
120 min. after	584	484	
Mrs. M. G.	23	212	395	395	Cerebral obesity.
120 min. after ingestion of 10 gm. of NaCl	00	430	
Mr. I. G.	42	332	(not estimated)	430	
120 min. after ingestion of 10 mg. of NaCl	500	410	Thyroövarian obesity.
Mrs. M. H.	41	204	400	380	
120 min. after ingestion of 10 gm. of NaCl	440	420	

It is noteworthy that the 2 patients who showed the retention of NaCl have lost considerable weight under the salt restriction and dehydration régime.

Di Foutsin³⁰ determined the NaCl after the administration of 15 to 35 mg. of NaCl in normal persons and found no difference between the capillary and venous blood during a period of 2½ to 4 hours.

To increase the water elimination in obese persons who fail to reduce on diet alone, we use Salyrgan intravenously, as first suggested by Eppinger.³¹ The diet is equivalent to approximately the basal caloric intake for a person of the desired weight. Thus, if the desired weight was 160 pounds, the patient's basal caloric intake would be approximately 1500 calories (20 calories per kilogram of body weight).

The amount of protein varies from 1 to 1½ gm. per kilogram of desired body weight (in this instance 108 gm.). The difference in

calories between carbohydrate and fat is divided in ratio of 1 to 3, or carbohydrate 35 and fat 105, in this instance. The carbohydrate may be increased to 0.5 gm. to each gram of protein. The high protein keeps the patient in nitrogen equilibrium, and with the low carbohydrate favors water elimination.

The ketogenic-antiketogenic ratio of such a diet is less than 1.5 to 1 and is well tolerated. The fluid intake is limited to 1000 to 1200 cc. per 24 hours and the salt is restricted to 5 to 7 gms. daily.

Theocin may be used, but we found it objectionable, since it is apt to cause gastrointestinal disturbance.

We begin with 0.5 cc. of Salyrgan; if the urine fails to show evidence of kidney damage such as red blood cells and casts, the dose is increased to 1 cc. twice a week for 1 week, then 1 cc. every week for 2 weeks, and later one injection every month until the desired results are obtained.

The case below illustrates the apparent efficacy of Salyrgan in the treatment of certain types of obesity.

CASE 1.—Mr. T. M., aged 38 years; height, 5 ft. 7 in.; weight, 291 pounds. The patient complains of inability to keep awake and of constant gain in weight. In the past year he gained 100 pounds. With the increase in weight his drowsiness increased; he also developed polyuria, urinating nine to ten times during the day and five times on an average during the night. He claims to void about $\frac{1}{2}$ pint of urine each time. He had influenza in 1917 and left otitis media in 1919. There was no history of obesity on either the maternal or paternal side of the family. He drinks large quantities of water during the day. According to his statement, his food is not excessive.

Physical Examination. The patient is a white male, aged 38 years, very obese, with marked tendency to girdle distribution. He has a short, thick neck. Body hair scanty; abdomen heavy and pendulous. The genitalia were normal.

Neurologic Examination (Dr. A. Silverstein). Pupils irregular, right reacts sluggishly to light. Labiofacial fold of right side less marked than left. Tremor of orbicularis muscle when patient shows his teeth. Upper extremities: Biceps and triceps reflexes markedly diminished, practically absent. Lower extremities: Knee jerks diminished on both sides. Some tenderness of fat deposits to palpation. All tests for sensation and cerebellar function were negative. The visual field examination was practically negative. The fundus examination (Dr. J. C. Rommel) shows that the media were clear; disks oval, the margins blurred and some swelling of the nerve head. Roentgen ray appearance of the sella turcica was normal. The basal metabolic rate was +30. Specific dynamic action of food 2 hours after mixed meal was 8(—) per cent. Sugar tolerance: Fasting specimen, 105.3; first hour after glucose, 148.1; second hour after glucose, 137.2; third hour after glucose, 80. Urinalysis: No abnormal findings. Blood chemistry: Sugar, 100; urea, 19; uric acid, 4.2; creatinin, 1.5. Sodium chlorid: Capillary blood was 350, venous blood 300. After 10 gm. of salt the capillary blood was 330 45 minutes later and 375 2 hours after. Venous blood, 300. Spinal fluid: Pressure, 8 mm. mercury; other findings negative. McClure-Aldrich test: Wheal disappeared in 7 minutes on forearm and 10 minutes on leg. Water retention: 500 cc.

The patient was placed on a diet of 1100 calories with restriction of fluids and salt. Diuretics, such as urea, have been used without apparent benefit. One cubic centimeter of Salyrgan was then given every 4 days for a period of 3 weeks. At the end of this period he had lost 29 pounds.

NOTE.—The patient had previously been in two hospitals with the hope of reducing his weight, but failed to lose any weight. He is still under observation and treatment in the Metabolic Clinic of the Temple University Hospital.

This case is apparently one of cerebral obesity. The symptoms of drowsiness and polyuria speak for a pathologic process in the region of the pituitary, infundibulum or paraventricular nuclei in the floor of the third ventricle. A mass lesion such as an intrasellar or suprasellar growth can be ruled out by the negative field studies and normal sella turcica by the Roentgen ray. In view of the fact that his symptoms of drowsiness and mental hebetude cleared considerably after the increase in fluid output would suggest that the hydrated condition of the brain was greatly lessened following treatment.

I used Salyrgan in 5 more patients with various types of obesity accompanied by water retention with good results.

An individual who retains water also has a tendency to deposit fat. Therefore, when he is dehydrated, he not only loses weight but is prevented from accumulating fat.

Water and salt metabolism, like temperature regulation, is governed by regulative centers in the central nervous system.

The polyuria and also glycosuria following a puncture in the floor of the fourth ventricle (Claude Bernard, 1835) are well known facts in point.

It was shown by Yungman and Erich Meyer³² (quoted by Greving) that a puncture in the neighborhood of the nucleus of the visceral vagus not only produces polyuria but also an increase in salt elimination. The increase of the salt elimination is independent of the increase in urine elimination. Brugh, Dresel and Lewy³³ believe to have shown that the centers for water and salt metabolism are present in the formatio reticularis.

There are centers in the hypothalamus for water and salt metabolism (Leshke). The exact location of these centers is not known. It is surmised that the centers are in the neighborhood of the supra-optic nucleus near the optic tract. Puncture of the caudate nucleus made by Reynolds and Spiegel³⁴ produced not only polyuria but also an increase of the salt elimination. This phenomenon was observed especially in those animals who showed also an elevation in temperature, proving that there is some relationship between the heat and salt and water metabolism centers.

The ability of the tissues to retain water is also believed to be regulated by certain centers in the central nervous system. The retention of water in the tissues is probably influenced by the

centers through the interaction of some of the glands of internal secretion.

We know that thyroxin diminishes water retention (Eppinger). The regulation of the water metabolism by the centers in the hypothalamus is therefore probably brought about through the action of endocrine glands. There is reason to believe that there are likewise centers in the hypothalamus for fat metabolism. The production of obesity in animals by injury to the hypothalamic region (tuber cinereum) without pituitary injury has been demonstrated by Smith.³⁵ The rôle that the pituitary gland plays in stimulating or inhibiting these centers is difficult to explain.

Raab³⁶ has shown that the injection of pituitrin is followed by an increased lipid content of blood, probably due to an increased production of fat in the liver for ready use by the tissues. By depressing the heat center with antipyretics he found that the pituitary extract had no effect on the increased fat metabolism. One, therefore, may draw the conclusion that part of the heat center is concerned with fat metabolism.

The exact rôle the pituitary gland plays in the production of obesity is not definitely explained. It is known that Simmond's disease (marked cachexia) may arise as the result of lesions in the anterior lobe of the pituitary. It is also known that disease in the posterior lobe may produce marked obesity. These findings, like many pituitary phenomena are difficult to reconcile.

Conclusion. In obesity, though the law of conservation of energy is operative, *i. e.*, the balance between energy intake and energy output is disturbed, on the surface it is not apparent in some patients because they seem to gain in weight in spite of a low intake of food. Disturbances in water and salt metabolism with storage of water in the tissues should be borne in mind in such cases. In such patients the higher centers for fat metabolism, salt metabolism and water metabolism may be maladjusted (as in encephalitis). In the latter case it may often be related to the action of the product of some gland or glands of internal secretion. Obesity of hypothyroid nature seems to be infrequent. That some endogenous factor exists that would seem to account for some forms of obesity cannot be denied. Whether the endogenous factor is of constitutional nature and is associated with an endocrine disturbance, or the obesity is causing the latter is difficult to prove. Each case of obesity is a problem in itself, with regard to the basic causation and treatment. The general lines of management will include proper diet, proper exercise, restriction of fluid and salt, and in certain selected cases the administration of thyroid preparations. In certain cases the administration of Salyrgan in addition to diet and water and salt restriction seems to yield satisfactory results.

NOTE.—I wish to acknowledge my indebtedness to Dr. D. Meranze and Dr. F. W. Konzelmann for their aid in the laboratory work during this study.

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THE CRAIG COMPLEMENT-FIXATION TEST FOR AMEBIASIS IN CHRONIC ULCERATIVE COLITIS.

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CHRONIC ulcerative colitis is an inflammatory disease of the lower intestine. It is characterized clinically by numerous rectal discharges of small liquid stools containing blood, mucus and purulent

exudate, also, by more or less fever, abdominal cramps, anemia, prostration and toxemia. It frequently terminates in the death of the patient from either toxic degeneration of vital organs, inanition, acute perforation, intestinal ileus or septicemia.

The chronic nature of ulcerative colitis, its resistance to treatment and the general failure to show a consistent etiologic factor have given rise to many speculations as to the initial cause of the disease. Some have considered the disease to be a chronic stage of bacillary dysentery. Shiga has reported that the bacillary disease may sometimes become chronic although the initial causative organism, which is very easily overgrown, may not be found after the first few days following the onset of the acute stage. Although the *Bacillus dysenteriae* does not persist long in the stools it would seem that the chronic cases would be more apt to show a specific agglutination reaction in the serum. Hawkins, however, did not find this to be true in the sporadic cases of ulcerative colitis occurring in England at least.¹ Silverman² has reported that apparently several strains of the bacilli of dysentery are accountable for sporadic cases occurring in the southern States. He was able to recover from such cases the bacilli of Shiga, Flexner, Morgan and Duval or Sonne, and agglutinating reaction supported the diagnoses. However, the clinical relationship between such cases and cases of the disease known as chronic ulcerative colitis is problematical. Hurst,³ having noticed a marked similarity in the proctoscopic appearances of the rectal mucosa in chronic bacillary dysentery and idiopathic chronic ulcerative colitis, reports that he treats all of his cases of the latter disease with specific antibacillus dysentery serum with "miraculous" results in some cases. He uses the serum in large intravenous doses producing, in many cases, marked foreign protein reactions. Since those who work with the acute bacillary disease have found that serum therapy is practically valueless after the first few days following the onset, it may be possible that the good results which Hurst obtains in the chronic condition are due to the nonspecific reaction to a foreign protein. The similarity of the proctoscopic appearances in the two conditions can be explained on the basis that both diseases are purulent inflammations of the mucous membrane with extension to the underlying tissues and in the chronic stage the process is so modified by secondary infection that the pathology in the colon becomes much the same.

Within the last few years the interest in the bacteriology of colon disease has been greatly stimulated by the work of Bargen^{4,5} of the Mayo Clinic. He has reported that in a large proportion of cases he has been able to isolate from the ulcerations in the colon a diplostreptococcus with fairly definite morphologic and cultural characteristics. Paulson⁶ has been able to isolate many different strains of enterococcus which will produce colitis in animals. Some of these strains were obtained from normal healthy individuals and

from infections outside the gastrointestinal tract. The bacteriology of the colon is a complicated difficult problem and much work has yet to be done before the bacterial etiology of ulcerative colitis is either definitely established or definitely disproved.

That chronic ulcerative colitis is a chronic form of amebic dysentery is another conjecture that has some features suggesting that it is within the realms of possibility. Amebic dysentery is now known to be more widely spread than was formerly realized and it has been fairly definitely proven that from 5 to 10 per cent of the population of the United States harbor the *Amœba histolytica*. Although in the early stages of amebic dysentery and ulcerative colitis the appearance of the mucosa as viewed through the sigmoidoscope may be sufficiently different to be diagnostic, in the later stages when superimposed secondary infection has greatly modified the amebic disease, it is almost impossible to make a differential diagnosis by means of the sigmoidoscopic examination.

In the acute case of amebic dysentery a competent protozoologist usually has no difficulty in demonstrating the etiologic agent, and in many of the chronic cases pathogenic amebæ are present in greater or lesser numbers. However, in some of the chronic cases the finding of either the vegetative forms or cysts becomes exceedingly difficult. Even material obtained by scraping the ulcers, a procedure which is often fruitful when the stools are negative, fails to show the amebæ in some definitely proven cases of amebiasis. In 2 of Councilman and Laffleur's⁷ cases amebæ were not found in the stools or in sections made of the intestinal ulcers, but were found to be present in liver abscesses. If the liver abscess had not been present a diagnosis of amebiasis would not have been justified even though the intestine was ulcerated. Hutchison⁸ also reports a case of amebic dysentery which came to autopsy which showed extensive ulceration of the colon, but no amebæ were found in any of many sections. Both Hutchison⁸ and Callender,⁹ in their papers on amebic dysentery, suggest as an explanation for this paucity of amebæ the prominent part that secondary infection plays in the chronic stage. They have found that the amebæ enter the tissues by lysis and with little leukocytic reaction. They spread through the lymph channels of the submucosa. The symptoms of dysentery arise when the initial lesion is invaded by secondary pyogenic organisms. The amount of destruction and reaction depends upon the character of the secondary invader, which causes the spread of the ulcer so that the tissue damage becomes out of all proportion to the number of amebæ present. Amebæ are always scarce in the presence of active suppuration and absent where there is granulation tissue. For this reason the failure to find amebæ in the stools is not sufficient evidence upon which to make a differential diagnosis.

The late changes in the colon are also much the same in the two diseases. The intestinal wall becomes much thickened with the formation of a straight, narrow, inflexible lumen. Polypi have been

reported to arise in the long-standing cases of both conditions with occasional carcinomatous degeneration.^{7,10}

Since a review of the literature indicated that there was nothing in either the clinical course of the disease, the microscopic examination of the stools, the bacteriologic examination of the infected material or the sigmoidoscopic examination of the intestinal mucosa that conclusively differentiated between chronic amebic colitis and chronic ulcerative colitis, the author has employed a complement-fixation reaction recently advanced by Craig as diagnostic of amebiasis. This test has been applied to the sera of 19 patients who clinically and sigmoidoscopically were characteristic cases of chronic ulcerative colitis and the real purpose of this paper is to report the results of this test in correlation with the results of other clinical and laboratory findings and with the results of anti-amebic therapy.

In a report on the results of his test, Craig¹¹ gives the results of the test on 689 patients. In 84 (12 per cent of this group) the complement-fixation test was 3+ or 4+ positive. Any reaction less than 3+ positive he considers undiagnostic. Of the 84 cases with positive complement-fixation test, 92 per cent showed *Endamoeba histolytica* in the stools. In the remaining 8 per cent the stools were possibly insufficiently examined. In the 605 cases with negative serologic findings the *Endamoeba histolytica* was present in only 0.8 per cent. The test, when applied to patients with acute or chronic diseases of other types and with other types of protozoal infections, gave uniformly negative results except in some patients with a positive Wassermann reaction.

In all instances reported in this paper the serologic tests were done by Dr. Craig's laboratory in the Army Medical School, on sera sent by mail from Boston to Washington. The stool examinations were made either personally or by the pathologic laboratory of the New England Deaconess Hospital under the direction of Dr. Shields Warren. In most instances the stools were examined both microscopically and culturally for amebæ by Dr. Lemuel R. Cleveland of the Harvard School of Tropical Medicine.

In our series of 22 cases which were diagnosed chronic ulcerative colitis by clinical, proctoscopic or postmortem examination, *Endamoeba histolytica* were found in the stools of 3. This does not include cases of definite amebic dysentery with characteristic amebic ulcers in the rectum and sigmoid.

These 3 cases all showed a positive Craig test. In the series there were, all told, 19 cases on whom the Craig test was done. There were 15 positives, that is, 4+ or 3+ reactions, which Craig considers diagnostic, and 4 with either negative, + or 2+ reaction, which are not diagnostic.

The 4 cases who gave a negative or only 1+ or 2+ reactions were not clinically different from the larger number of cases giving a definitely positive reaction.

Case No.	Age.	Sex.	Symptoms.	Severity by proctoscopy.	Extent by Roentgen ray.	Comple-ment-fixation.	Treatment.	Duration of follow-up; results.
1 (6681)	21	F	Bloody diarrhea for 10 weeks; fever; prostration; amebæ in stools	Not done	Entire colon	++++	Antiamebic drugs; transfusion; ileostomy	Death from toxemia; autopsy showed typical ulcerations of colitis but amebæ in tissues.
2 (14817)	38	F	Recurrent bloody diarrhea since childhood; anemia; amebæ in stools	++ Polypoid	Entire colon	++++	Treatment refused	
3 (14044)	54	M	Recurrent bloody diarrhea for 25 years; marked anemia; no amebæ in stools	++	Entire colon	++++	Diet; iron; antiamebic drugs	16 months; excellent remission; no recurrence.
4 (14693)	37	F	Recurrent bloody diarrhea for 5 years; anemia; no amebæ in stools	++	Entire colon	++++	Diet; antiamebic drugs	16 months; fair remission with 3 recurrences and stenosis of rectum.
5 (12832)	26	F	Stenosis of rectum; anemia; history of bloody diarrhea; no amebæ in stools	Not done	Sigmoid and rectum	+++	Ileostomy; diet; iron	18 months; rectal abscess with recovery; condition very good.
6 (16620)	38	F	Bloody diarrhea for 3 months; prolapse of rectum; anemia; no amebæ in stools	++	Entire colon	++++	Diet; iron; antiamebic drugs	Not heard from since; good remission.
7 (14585)	8	M	Bloody diarrhea for 10 months; anemia; no amebæ in stools	++	Entire colon	++++	Diet; antiamebic drugs	16 months; excellent remission; no recurrence.
8 (14600)	46	F	Bloody diarrhea for 6 months; loss of weight; no amebæ in stools	Normal	Ascending and transverse	++++	Diet; antiamebic drugs	12 months; improved; some recurrences of diarrhea; gain in weight.
9 (16506)	31	M	Bloody diarrhea for 4 years; no amebæ in stools	+++ Carcinomatous degeneration	Rectum	++++	Resection of rectum	12 months; complete relief; (epidermoid carcinoma).

10 (16930)	46	M	Recurrent bloody diarrhea for 20 years; anemia; fever; no amebæ in stools	++	Entire colon	++++	Diet; antiamoebic drugs; transfusion	12 months; good remission; no recurrences.
11 (16562)	25	F	Bloody diarrhea for 7 months; anemia; no amebæ in stools	++	Entire colon	++++	Diet; antiamoebic drugs	9 months; excellent remission; no recurrence.
12 (17706)	20	F	Bloody diarrhea for 4½ months; vomiting; fever; anemia; no amebæ in stools	++	Entire colon	++++	Diet; sedatives; antiamoebic drugs; transfusion	11 months; improved, but still has some diarrhea and bleeding.
13 (17705)	37	F	Diarrhea for 1 year; fever; prostration; anemia; amebæ present	++	Entire colon	++++	Diet; antiamoebic drugs	10 months; improved with occasional diarrhea.
14 (21122)	30	F	Bloody diarrhea for 9 weeks; vomiting; fever; moribund	Not done	Not done	++++	None	Death from perforation; autopsy; marked ulceration and necrosis of colon; no amebæ found.
15 (21030)	48	F	Bloody diarrhea for 2 months; fever; prostration; anemia; no amebæ in stools	Normal	Ascending colon	++++	Diet; antiamoebic drugs; transfusion	1 month; good remission.
16 (7529)	48	M	Recurrent bloody diarrhea for 26 years; fever; prostration; no amebæ in stools	++++	Entire colon	+	Diet; vaccine; ileostomy.	Death from toxemia; no autopsy.
17 (8268)	42	F	Bloody diarrhea for 5 months; anemia; no amebæ in stools	++	Entire colon	++	Ileostomy; antiamoebic drugs	28 months; improved; several recurrences.
18 (19854)	25	F	Diarrhea for 3 months; fever; prostration; no amebæ in stools	Normal	Ascending and transverse	+	Ileostomy	6 months; bloody rectal discharge; condition excellent.
19 (20306)	62	F	Recurrent bloody diarrhea for 1 year; no amebæ in stools	+	Entire colon	+	Diet; other treatment not tolerated	1 month; some improvement.

Besides the 19 cases of ulcerative colitis we have seen 3 other patients who gave a 4+ complement-fixation test. All 3 of these patients suffered from abdominal distress and intermittent attacks of diarrhea, but the stools were negative for blood or for the amebæ. One of them gave a history of a definite attack of acute amebic dysentery occurring in the tropics a few months previously and it is doubtful if she was entirely cured. The second patient had had attacks of diarrhea for years without gross blood being noticed at any time. The third patient died of chronic diarrhea and inanition and the autopsy showed no evidence of amebic infection or of ulcerative colitis.

We have also sent to Dr. Craig several sera from patients with diarrhea caused by functional disorders of the colon and he has reported them consistently negative.

We have also had one patient with diarrhea and *Amœba histolytica* in the stools who gave only a 2+ reaction.

The results of treatment of chronic ulcerative colitis are far from satisfactory, and no form of therapy yet tried has given uniformly good results, although almost any form of treatment will apparently bring about improvement in a certain proportion of cases.

The author is of the opinion that many clinicians throughout the country have used antiamebic drugs in cases of chronic ulcerative colitis even though they have been unable to demonstrate the ameba in the rectal discharges. It would be interesting to know in what percentage of cases such drugs have proved to be beneficial. We have treated most of our cases with emetin intramuscularly, acetarsone or stovarsol and bismuth by mouth, and in a few cases yatren has been used as a rectal infusion. In conjunction with these drugs we have used a low residue, high vitamin, bland diet and have used belladonna and opium in small quantities. Great caution should be exercised in basing any conclusions on the apparent benefit of any given form of treatment in a disease such as this. It may suffice to say that antiamebic drugs were used in 11 cases in this series. Four of these have had a complete remission of symptoms for from 10 to 14 months. Five others have been definitely improved but still have some diarrhea with occasional bleeding. One other has not been much improved but has not taken much treatment and has only been followed for 1 month. The other is at present under treatment in the hospital and is apparently recovering satisfactorily.

Although there is no proved relationship between ulcerative colitis and intestinal amebiasis, we believe antiamebic treatment should be tried in all cases suitable for medical treatment. The significance of the Craig test when amebæ cannot be found in the stools is still very much unsettled, but the results of the test when applied to cases of chronic ulcerative colitis are reported here with the hope that they will shed some light either upon the disease in

question or upon the specificity of the test itself. Craig admits that the serologic test which he has devised is difficult, and unless closely controlled is apt to give erratic results. It undoubtedly will require further verification before its actual value can be determined, particularly since his antigens are not made from bacteria-free cultures of amebæ. It may be that the positive reactions obtained in ulcerative colitis have more to do with a bacterial antigen than with the amebic antigen. On the other hand, the concept that ulcerative colitis is a superimposed secondary infection of a primary amebic ulceration of the colon seems to be within the realms of possibility, particularly since British soldiers serving in Egypt and Gallipoli have been known to suffer an acute attack of amebic dysentery with apparent recovery, and later to develop a chronic ulcerative colitis from which only streptococci could be obtained.¹² Whether or not the secondary bacterial invader is always the same is another phase of the complicated question. It may be that a specific organism, normally resident in the human intestine, sets up an inflammatory process in the intestinal wall only when certain opportunities such as an amebic ulceration occur.

Summary. That it is extremely difficult to differentiate between chronic ulcerative colitis and chronic amebic colitis has been pointed out and discussed.

The result of the Craig complement-fixation test for infection with *Endameba histolytica* when applied to patients with chronic ulcerative colitis is reported showing that 15 out of 19 cases gave a strongly positive reaction.

No conclusions as to the significance of this finding are drawn, but it is suggested that chronic ulcerative colitis may be a pyogenic infection of the colon superimposed upon an original amebic ulceration.

Abstracts of the case histories of the 19 cases tested are reported.

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A STUDY OF THE CAPILLARY PRESSURE IN NEPHRITIS AND HYPERTENSION.

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THIS investigation represents a further attempt to correlate variations of the blood pressure within the minute vessels with the clinical findings in acute and chronic nephritis and in essential hypertension. Special attention has been given to the influence of capillary pressure on the development of edema.

Many methods are available for the study of the blood pressure of the capillary. As in previous work,^{1,2} the closed capsule method³ has been used in making individual readings while visualizing the capillary at the base of the nail by means of a binocular microscope. The hand is kept at the level of the heart and constant temperature conditions are maintained. The pressure is read when the flow of blood is reestablished upon releasing the obstructing pressure in the closed capsule. Many observations were made, but only the most frequently recurring reading has been charted. Although the accuracy of the method has been questioned, Landis⁴ has shown by means of intracapillary pipettes that the blood pressure at the bend of the capillary loop corresponds with those made by the indirect method.

The same apparatus has been used in determining the venule pressure in the subpapillary plexus. It is agreed that the color of the healthy skin is dependent largely upon the blood in the subpapillary venous plexus. To read the pressure of the venules, the capsule is first inflated until the skin is rendered colorless. Reducing the pressure slowly, at the first appearance of color in the skin the pressure is read on the manometer and considered the venule pressure. These readings on normals have been found to correspond to those of Landis obtained in the venous limb of the capillary. This method differs from that of Lewis and Hynal⁵ in the criterion used in reading the pressure. These authors made their reading at the first diminution in skin color, determining in this way the amount of pressure necessary to overcome the resistance of the venule wall. The method employed in our studies gives the pressure necessary to reestablish the bloodflow, the procedure used in determining the pressure in the brachial artery. Several opportunities arose where it was possible to make pressure readings by observation of the bloodflow in the venule. These readings have differed only by 1 or 2 mm. of mercury from those found by the blanching method.

TABLE I.—HYPERTENSION CASES.

Hospital No.	Case No.	Age, yrs.	Vascular system.			Urine.			Hemoglobin, per cent.	R.b.c., millions.	Kidney function.		Serum protein, per cent.	Capillary pressure, mm. Hg.	Capillary morphology.	Venule pressure, mm. Hg.	Edema.	Notes.
			Eye grounds.	Radial.	B.P.	Alb.	R.b.c.	Cast.			2-hr. phthal.	Urea, mg. per 100 cc.						
130600	3	35	Neg.	Neg.	145/90	s.p.t.	Occ.	0	85	4.5	65	23	8.1	15	Slight tortuosity	..	0	PH tox. of pregnancy.
232419	6	41	A++++*	Neg.	255/140	0	0	0	100	6.0	60	22	8.1	10-15	Small, beaded, narrow arterial limb	..	0	
238765	7	19	160/90	89	5.1	..	18	7.9	30	Narrow arterial limb, rapid flow	..	0	
207798	35	..	Slight A*	A+*	168/120	0	0	0	..	5.7	55	22	7.2	25	Tortuous and normal types	..	0	
181448	48	33	A+*	Neg.	200/120	t.	+	0	93	5.5	65	38	6.7	28	Normal	15	0	
260175	48A	33	A+*	+	250/140	f.t.	0	0	93	5.4	75	24	7.4	25	Normal	15	0	
185742	23	30	...	Neg.	210/120	v.f.t.	Occ.	..	85	5.2	..	28	7.4	25	Large narrow arterial and wide venous loops	..	0	
71187	26	43	A+*	A+*	210/160	v.f.t.	0	Occ.	..	4.2	55	45	7.4	25	Narrow, rapid flow	12	0	
71296	29	35	Exudate	Neg.	240/130	v.f.t.	0	Occ.	..	4.7	65	26	7.1	25	Dilated and tortuous	5	0	Hand red.
88738	30	12	A+++*	Neg.	148/80	0	0	0	..	5.1	65	25	Dilated venous limb	12	0	Bier's spots on arm.
48653	41	45	A+*	A+*	230/140	v.f.t.	0	0	..	5.8	46	32	7.0	30	Narrow arterial limb	12	0	
255353	42	..	Exudate	Neg.*	200/110	f.t.	0	0	90	5.5	60	33	..	20	Narrow arterial limb	15	0	
61277	43	36	A++++	A+++*	180/125	f.t.	+	0	..	5.5	60	26	..	35	Normal	18	0	

* A = arteriosclerosis.

TABLE 2.—ACUTE NEPHRITIS CASES.

Hospital No.	Case No.	Age, yrs.	Vascular system.		Urine.			Hemoglobin, per cent.	R.b.c., millions.	Kidney function.		Serum protein, per cent.	Capillary pressure, mm. Hg.	Capillary morphology.	Venule pressure, mm. Hg.	Edema.
			Radial.	B.P.	Alb.	R.b.c.	Casts.			2-hr. phthal.	Urea, mg. per 100 cc.					
237003	8	10	Neg.	110/70	+	+	+	75	2.8	40	30	6.5	15	Normal, rapid	...	0
33338	13	26	Neg.	130/85	+	+	+	90	6.6	50	28	8.1	30-35	Small, tortuous	...	0
32305	37	26	Neg.	130/90	+	+	+	...	5.8	55	28	7.4	20-25	Normal	10	0
25211	47	19	Tense	115/70	+	+	+	...	4.0	4.1	30	Venous limb dilated	15	0
237003	25	19	Neg.	110/80	+	+	+	...	4.0	6.6	35	Long, narrow arterial limb	10	0
252134	39	...	Neg.	100/130	v.h.t.	+	+	105	5.7	15	54	4.2	30	Narrow arterial limb, flow rapid	15	+
280338	39A	...	Neg.	135/95	v.h.t.	+	+	51	3.0	70	90	5.9	20	Beaded flow	8	0
	N9	...	Neg.	140/90	h.t.	+	+	83	4.1	...	37	...	35	Normal	20	0

TABLE 3.—CHRONIC NEPHRITIS CASES.

Hospital No.	Case No.	Age, yrs.	Vascular system.			Urine.			Hemoglobin, per cent.	R.b.c., millions.	Kidney function.		Capillary pressure, mm. Hg.	Capillary morphology.	Venule pressure, mm. Hg.	Edema.	Notes.
			Eye grounds.	Radial.	B.P.	Alb.	R.b.c.	Casts.			2-hr. phthal.	Urea, mg. per 100 cc.					
12837	5	29	A*	A**	150/100	f.t.	+	+	83	4.8	53	46	6.3	Normal	25	0	
10839	11	30	A*	A**	210/120	t.	+	+	85	4.6	45	58	5.8	Many dilated	35	0	
14483	12	27	Neg.	Neg.	126/100	t.	+	+	110	6.4	60	28	7.2	Large tortuous arterial limb narrow, flow slow	30-35	0	
84270	14	18	Neg.	Neg.	110/60	t.	+	+	80	5.0	70	22	7.2	Arterial limb narrow	20	0	
244825	15	30	Neg.	Neg.	230/150	t.	+	+	...	5.5	45	31	7.8	Few with narrow arterial limb	30	0	
247105	18	28	A*	A**	220/160	h.t.	0	+	...	4.4	18	40	6.4	Narrow equal limbs	40	+	Py elampsia, 2 wks. ago had spontaneous abortion of 2 mos. pregnancy; terminal uremia.
18A	18A	230/130	h.t.	+	+	103	6.3	Thread-like	50	0	Chr. sinus infection.
242072	20	32	Neg.	Neg.	120/95	0	+	+	85	5.0	55	32	6.8	Normal	20-15	0	
69310	21	21	Neg.	Neg.	130/80	t.	+	+	85	5.6	60	31	0.8	Normal	25	0	
71905	22	27	A*	Neg.	220/130	t.	+	+	62	3.1	7	90	5.8	Tortuous	35	+	
217007	33	...	A**	A**	112/70	t.	+	+	50	5.8	...	250	5.6	Slight tortuosity, flow rapid	45	0	Recurrent hydrothorax; ph. hypertensive toxemia of pregnancy.
201816	40	...	Neg.	Neg.	115/85	t.	+	+	60	4.0	65	38	4.3	Narrow, slight tortuosity	20	0	

215431	50	210/140	t.	+	+	88	5.4	50	48	..	20	Large, dilated capillaries	20	0	Vasomotor spasm of hands.
57385	51	..	Neg.	130/75	t.	0	0	96	5.1	55	39	6.7	22	Large, dilated capillary	15	0	
54474	52	..	A**	125/80	t.	+	+	95	5.6	55	45	6.8	25	Arterial limb slight narrowing	20	0	
244825	54	..	A**	230/150	h.t.	+	+	101	5.9	65	29	7.2	35	Arterial limb slight narrowing	10	0	
194269	24	..	Neg.	100/60	t.	0	0	101	5.9	65	29	7.1	25	Flow is slow	10	0	Hand cool.
63581	27	33	A*	130/70	t.	+	+	75	4.0	15	59	..	15	Slight tortuosity	15	0	1 week ago acute pharyngitis.
256033	38	..	A**	190/84	h.t.	+	+	90	3.5	50	39	7.1	35	Narrow, not numerous	12	0	Terminal uræmia.
242134	28	22	A***	200/150	t.	+	+	90	4.6	45	39	7.1	35	Venous limb dilated	8	+	Transfusion last week.
28A	28A	180/130	h.t.	+	+	80	4.3	60	61	5.0	20-25	Arterial limb narrow, flow slow	..	+	
84878	1A	..	Neg.	130/90	t.	0	0	61	3.2	60	30	4.0	25	0	
1B	1B	120/90	t.	0	0	83	4.5	6.0	25	+	
1C	1C	140/110	t.	0	0	70	3.8	6.0	30	Few capillaries; venous limb dilated	..	0	Nervous and pale.
75508	10	..	Neg.	180/110	f.t.	+	+	50	2.2	..	68	6.1	40	Arterial tortuous venous limb dilated	20	0	
241392	45	..	Neg.	180/110	t.	+	+	95	4.3	22	40	6.3	35	Both limbs narrow, rapid flow	25	2	
277228	N1	..	Neg.	140/100	h.t.	0	0	70	3.6	..	14	5.6	50	Narrow-beaded flow	15	2	Sinus infection.
75211	N2	110/70	h.t.	+	+	70	3.2	..	53	4.7	28	Narrow rapid flow	20	1	Sinus infect. clearing.
75568	N3	..	Neg.	120/80	h.t.	Occ.	Occ.	45	2.5	4.7	35	Normal-beaded	25	1	
279754	N4	..	+	148/105	h.t.	+	+	96	4.5	..	35	6.4	35	Rapid, beaded	20	0	Acute sinusitis; t. 100.
279754	N5	..	A*	190/130	h.t.	+	+	96	4.5	..	41	5.6	20	Normal, slow	10	1	Rhinitis.
242073	N6	135/90	h.t.	+	+	84	4.2	..	51	4.8	30	..	15	0	
242073	N7	110/90	t.	+	+	86	5.4	..	4	6.0	45	Narrow, rapid	25	2	
280319	N8	36	A**	200/180	h.t.	+	+	73	3.8	20	4	6.0	45	0	

* A = arteriosclerosis.

TABLE 4.—CARDIAC DECOMPENSATION CASES.

Hospital No.	Case No.	Age, yrs.	Sex	B.P.	Radial	Eye grounds	Urine	Capillary pressure, mm. Hg.	Serum protein, per cent.	Kidney function.	Capillary morphology.	Venule pressure, mm. Hg.	Edema.
1336	55	64	A**	210/100	++	A**	0	40	5.5	59	Venous limb dilated	40	+++
55A	55A	180/100	0	45	5.6	65	..	40	+++
69047	58	34	Neg.	180/100	Neg.	Neg.	+	28	..	36	..	28	+

* A = arteriosclerosis.

The osmotic pressure of the blood is determined by the amount of its crystalloid and colloid constituents. The crystalloids can be ignored as they are counterbalanced in the tissue spaces in accordance with the Donnan equilibrium. The effective osmotic pressure of the serum is dependent upon the concentration of its protein fractions—albumin, globulin and fibrinogen. In our studies the total serum protein concentration was measured.

The cases studied have been grouped according to clinical diagnosis, and together with physical and laboratory findings, tabulated in Tables 1, 2, 3 and 4.

Results. In the group of patients with essential hypertension no typical capillary morphology was found, *i. e.*, neither the shapes of the capillaries nor the type of bloodflow was distinctive. The arterial limb was usually narrower than the venous limb. The presence of scleroses in the radials or retinal vessels was not constantly associated with any tortuosity or other characteristic change in the form of the capillary. The height of the brachial and capillary pressures showed no constant relationship. The capillary pressure in this series of cases was found in most instances to be near the upper limit of normal, although in a few it was abnormally increased. Neither the cases with high or normal capillary pressure presented any associated significant physical or laboratory findings. The serum proteins were normal in concentration and no edema was present.

The cases of acute nephritis were either in an active or a convalescent stage. The radials and retinal arteries showed no abnormality. No constant morphologic change was present in the capillaries in either stage. The eye grounds were negative in every case. In Case 39 there was severe renal bleeding of 3 days' duration. Table 5 shows that the active cases had blood and albumin in the urine and that their capillary pressures were increased in all instances. Edema was present where the increased capillary pressure was associated with a low serum protein. The venule pressures were normal.

In the cases of chronic nephritis the capillaries though often tortuous presented no consistent morphology, nor did they show any constant relationship to the state of the peripheral vessels. The cases as analyzed in Table 6 fall into two groups, either a normal or a high capillary pressure. Hematuria was present in about one-half of the first group and in about two-thirds of the patients of the second group. By far the greater number of cases with poor kidney function had a high capillary pressure. Thirteen cases had edema. Ten of these patients had a high capillary pressure which was associated in 3 instances with a low serum protein, in 6 with slightly decreased serum protein and in 1 with a normal protein concentration. To show more clearly how the variations in degree of edema were associated with coincident variations in capillary

TABLE 5.—ACUTE NEPHRITIS.

	Blood pressure, mm. Hg.	Capillary pressure, mm. Hg.	Serum protein, per cent.	Edema.	Venule pressure, mm. Hg.
		<i>Active Cases.</i>			
39 . . .	160/130	30	4.2	+	15
47 . . .	115/70	30	4.1	+	15
25 . . .	110/80	35	6.6	0	10
13 . . .	130/95	30	8.1	0	
N9 . . .	140/90	35	5.9	0	20
		<i>Convalescent Cases.</i>			
37 . . .	100/90	20	7.4	0	10
8 . . .	100/70	15	6.5	0	

TABLE 6.—CASES OF CHRONIC NEPHRITIS.

No.	Blood pressure.	Capillary pressure.	Serum protein, per cent	Edema.	Urine.		Kidney function.
					Alb.	R.b.c.	
27 . . .	130/70	15	..	0	t.	1	Markedly impaired.
14 . . .	110/60	20	7.8	0	t.	0	Normal.
20 . . .	120/95	20	6.8	0	0	1	Normal.
49 . . .	115/85	20	4.3	0	t.	1	Normal.
50 . . .	210/140	20	..	0	t.	1	Normal.
N6 . . .	135/90	20	5.6	0	h.t.	1	Normal.
51 . . .	130/75	22	6.7	0	t.	0	Normal.
5 . . .	150/100	25	6.3	0	f.t.	0	Normal.
21 . . .	130/80	25	6.8	0	t.	1	Normal.
32 . . .	112/70	25	..	0	t.	1	
52 . . .	125/80	25	6.8	0	t.	0	Normal.
24 . . .	100/60	25	7.1	0	t.	0	Normal.
28a . . .	180/130	25	5.0	1	h.t.	1	Markedly impaired.
1a . . .	130/90	25	4.0	1	t.	0	Impaired.
1b . . .	120/90	25	6.0	0	t.	0	Impaired.
N2 . . .	110/70	28	4.7	2	h.t.	2	Impaired.
15 . . .	230/150	30	7.2	0	t.	1	Normal.
1c . . .	140/110	30	6.0	1	t.	0	Impaired.
N7 . . .	110/90	30	4.8	1	t.	2	Impaired.
11 . . .	210/120	35	5.8	0	t.	1	Impaired.
12 . . .	126/100	35	7.2	0	t.	1	Normal.
22 . . .	220/130	35	5.8	1	t.	0	Markedly impaired.
54 . . .	230/150	35	7.2	0	h.t.	1	Normal.
28 . . .	200/150	35	7.1	0	t.	2	Markedly impaired.
45 . . .	180/110	35	6.3	0	t.	3	Impaired.
N3 . . .	120/80	35	4.7	1	h.t.	1	Impaired.
N4 . . .	148/105	35	6.4	1	h.t.	2	
N5 . . .	190/130	35	4.0	3	h.t.	1	Normal.
18 . . .	220/160	40	6.4	0	t.	0	Markedly impaired.
38 . . .	190/84	40	4.4	0	h.t.	1	Markedly impaired.
10 . . .	180/110	40	6.1	0	f.t.	1	Markedly impaired.
33 . . .	140/100	45	5.6	1	t.	0	Markedly impaired.
N8 . . .	290/130	45	6.0	2	h.t.	2	Normal.
18a . . .	230/130	50	6.3	1	h.t.	0	Markedly impaired.
N1 . . .	140/100	50	5.6	2	h.t.	0	Markedly impaired.

pressure and serum protein, the clinical course of Case 33 is graphically presented in Chart I. The theoretical significance of this will be discussed later. An opportunity arose during this investigation to note in several cases a difference in response of the capillary pressure to stress during the course of their disease. Case 28, after a 2 months' pregnancy, had a rise in capillary pressure, the hypertensive reaction usually found in toxemias of pregnancy. Cases 18, N1 and N2, following an acute pharyngitis, had a drop in capillary pressure. The clinical picture, however, in both types was similar.

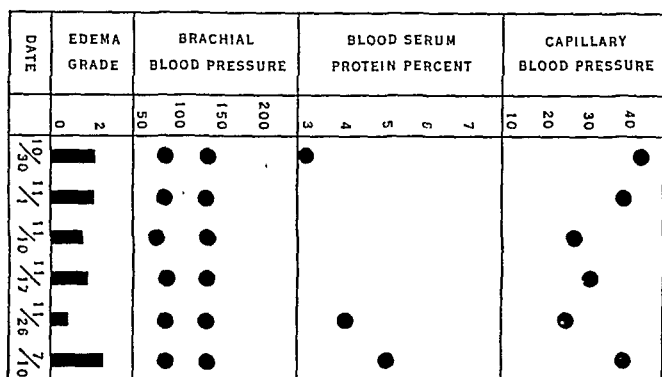


CHART I.—Case 33. Graphic relationship of edema and other factors.

In the cases of nephritis with cardiac failure studied the venule pressure was increased to the level of the capillary pressure, which in 1 case was normal and in the other was abnormally high. The increase in venule pressure in cardiac decompensation has been observed by other investigators.

Discussion. The literature concerning capillary morphology in hypertensive disease is extensive. A beaded type of bloodflow and varieties of shapes of loops during the active illness have been described⁶ with a return to normal upon the subsidence of the clinical condition. Our observations have not confirmed these findings. However, the capillary morphology has helped explain the pallor that is present in the patients with a nephrotic type of renal disease. The pallor is much more marked than one would expect from the hemoglobin and red blood cell count. The capillaries were found to be few in number and so threadlike in diameter that it has been impossible to make pressure readings on them. A case of pernicious anemia with a similar grade of pallor showed many more capillaries at the nail base. The pallor appears to be due to a paucity and extreme contraction of skin capillaries resulting in a decreased flow of blood in the skin. Whether these capillaries are in a spastic state or are permanently narrowed is difficult to say.

From a consideration of the morphology and blood pressure of the capillaries in the cases of essential hypertension as reported here and elsewhere, it is difficult to concede that essential hypertension is due solely to arteriolar spasm. It is a physiologic principle that distal to a constriction of a lumen there is dilatation. During the course of the work here reported several cases of Raynaud's disease in which there is a true arteriolar spasm limited to the extremities were studied. Chilling of the hand causes a typical

TABLE 7.—RAYNAUD'S DISEASE.

Hospital No.	Case.	Temperature.	Capillary pressure, mm. Hg.	Venule pressure, mm. Hg.	Appearance of capillary.	Note.
186143	1	Warm	12	14	Large	Cyanosed.
		Cold	5	5	No change	
229166	2	Warm	...	8	Narrow	Cyanosed. Skin white after closing hand once.
		Cold	...	15	Dilated	
		Cold	...	2	Dilated	
276859	3	Warm	...	15	Large venous limb	Skin dusky.
		Cold	...	5	No change	
275909	4	Warm	10	15	Narrow	Skin dusky.
		Cold	0	10	Dilated	
251852	5	Warm	15	...	Narrow	White hand.
		Cold	5	...	No change	

attack, during which the capillaries at the nail base dilate and both the capillary and venule pressures fall. If essential hypertension is the result of an arteriolar spasm a similar type of reaction might be expected, even if not as intense. This was not found to be the case. The capillaries are narrow, especially their arterial limb, the flow of blood is normal or more rapid and the capillary and venule pressures are increased or near the upper limits of normal. This picture suggests that in essential hypertension there is a generalized constriction of the vascular tree.

The blood pressure of the capillary can vary independently of the rest of the vasomotor system. The capillary helps sustain the pressure head of the circulation by means of its contractile Rouget cells. It is sensitive to changes in oxygen content of the blood,⁷ to variations in temperature and to chemical and mechanical stimulation. The pressure has been shown to be increased in some cases of hypertension,¹ frequently in acute and chronic nephritis^{1,2,8,16} and the hypertensive toxemias of pregnancy.^{2,9,10} It has been noted that the increase is associated with the active phase of the illness, the pressure returning to normal with convalescence; and the idea has become prevalent in the literature that the significant feature of these clinical conditions is a generalized capillary involvement.

In our work all the cases of acute nephritis had a high capillary pressure with blood and albumin in the urine, all disappearing in convalescence. A large majority of the cases of chronic nephritis with a high capillary pressure had albumin and blood in the urine. Furthermore, those with a marked hematuria were limited to the increased pressure group. This association of increased capillary pressure and urinary signs during the active stage of the disease is indicative of a systemic capillary involvement.¹⁹ The significance of these findings may be clarified by a recent study¹¹ on the mammalian capillaries in the sartorius muscle. The typical reaction to any but harmful stimuli was dilatation. Vasoconstriction was the response to severe irritants which finally lead to endothelial destruction. In view of this statement the vasoconstriction or high capillary pressure found in the cases of nephritis suggests that there is a generalized stimulation of the capillary endothelium.

The capillary pressure is an indicator of the balance between the driving force of the bloodflow and the resistance of the vascular wall. The osmotic pressure is a measure of the attraction of the constituents of the blood serum for water. The endothelium is a semipermeable membrane of extreme thinness, being only slightly permeable to protein. Filtration of fluid from the blood to the tissue spaces takes place when the capillary pressure exceeds the osmotic pressure and resorption when the latter is greater. The rate of interchange depends upon the degree of difference in the two pressures. The normal capillary is the site of both these processes. Landis⁴ has shown that in the arterial limb of the capillary the blood pressure exceeds the osmotic pressure, and that in the venous limb these relations are reversed. An exaggeration of this normal relationship, due either to an increase of capillary pressure or a decrease in osmotic pressure, will result in edema. When the endothelium is injured the rate of fluid loss is increased as much as four times.⁷ This increase in permeability can be brought about by adding endothelial poisons to the blood or by deoxygenation of the experimental animal. To study the effects upon the human endothelium of a similar injury, patients in whom an intense anoxemia could be brought about were examined. When their oxygen administration was stopped cyanosis became intense, the capillary blood pressure fell abruptly and the rate of flow was reduced. With restoration of oxygen the pressure rose. Koranyi¹² believes that additional influences on the transudation of fluid are chemical and hormonal changes in the blood. Further, he feels that the protein content of the edema fluid slows the rate of flow through the capillary endothelium.

Clinically, the relationship of low osmotic pressure to edema has been emphasized first by Epstein¹³ and others, but the rôle of the capillary pressure has been neglected. Cases are often seen in which edema is present with a normal serum osmotic pressure.

These exceptions were discussed in a recent paper¹⁴ on edema and low serum protein, but in this case, too, the capillary pressure has been disregarded. Following the original conception of Starling, Krogh¹⁵ and later Landis⁷ have shown that changed values in both these pressures are requisite factors in loss of water from blood to tissue spaces. Two clinical studies have recently been reported confirming this. However, Nakazawa and Izumi¹⁶ have calculated

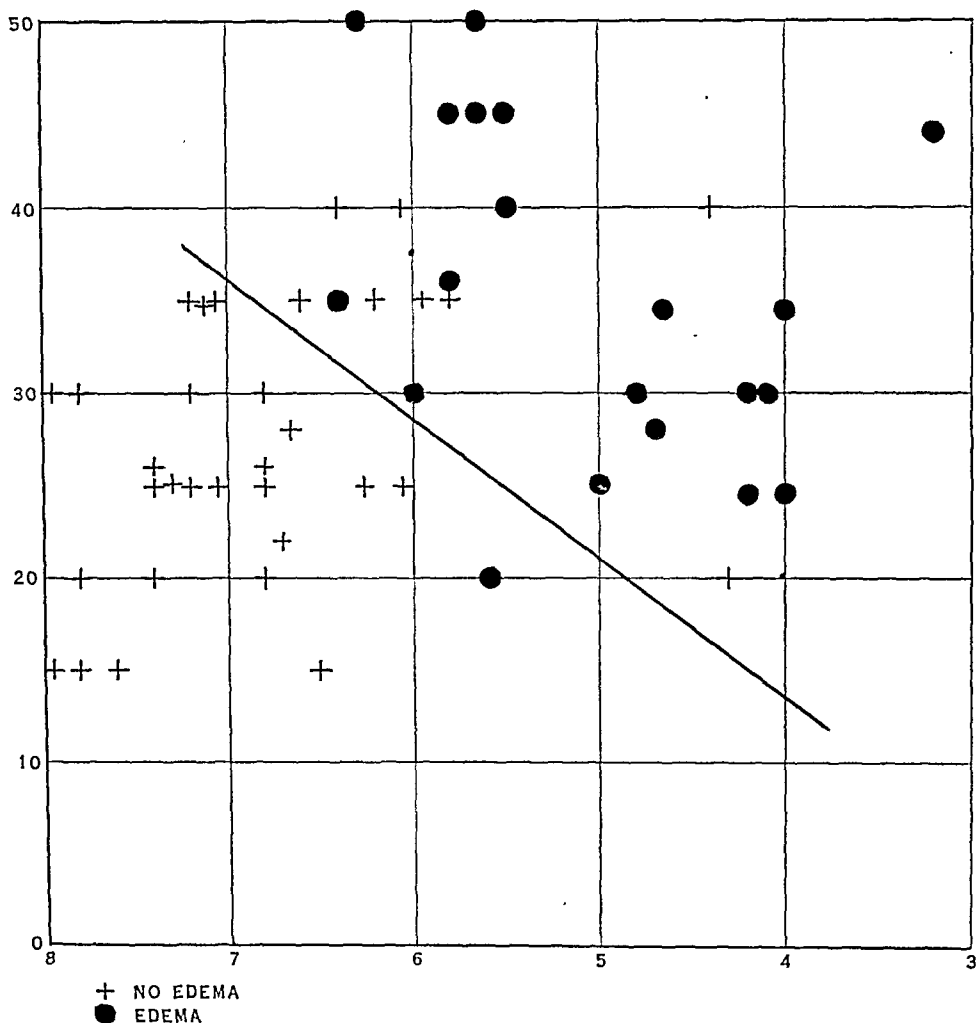


CHART II.—Relationship of capillary pressure and serum protein per cent to edema.

capillary pressures from that of the brachial artery. This is not a justifiable assumption, as in all the previous and present work it has been emphasized that there is no mathematical relationship between the two. In the work of von Farkas¹⁷ the capillary pressure was calculated from the venous pressure. This method has not been found correct.¹⁸ Von Farkas found the venous pressure normal in cases of nephritis with edema and high when there was an associated cardiac decompensation. However, Koranyi feels that in

spite of the low venous pressure the capillary pressure is higher than the osmotic pressure of the blood plasma.

An analysis of the cases with edema would indicate that the blood pressure of the capillary is an important factor. In the presence of a very high capillary pressure edema will result even though the osmotic pressure is normal or a low normal. To visualize the interrelationship of these two pressures to the presence or absence of edema all the cases reported in this paper have been plotted in Chart II. It shows the serum protein per cent on the abscissa and the capillary pressure on the ordinate. Study of this graph shows that the vast majority of the cases with edema group themselves in the upper right side; those without edema fall in the lower left side. A line can be drawn separating these well-defined groups, and it appears to lie just above an imaginary line which connects the points at which both the pressures are balanced and fluid interchange is at a standstill. There was only one marked exception in the nonedematous group; however, doubt was cast upon the accuracy of its serum protein, as on many subsequent examinations it was found to be normal.

In the cases associated with cardiac insufficiency both the arterial and venous limbs contribute to the formation of edema. The pressure is high in both, and not only is there increased fluid loss from the blood but delayed absorption from the tissue spaces.

Summary. 1. A comparison has been made between the capillary morphology found in essential hypertension and peripheral arteriolar spastic (Raynaud's) disease. From their marked difference it seems more probable that essential hypertension is due not solely to arteriolar spasm but to a generalized arterial spasm.

2. The frequent association of high capillary blood pressure with renal disease is indicative of a spasm response due to a severe involvement of the systemic capillary system.

3. A relationship between the capillary pressure and osmotic pressure of the blood to the presence of edema has been found to exist in nephritis.

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THE PRACTICAL APPLICATION OF THE BLOOD SEDIMENTATION TEST IN GENERAL MEDICINE.*

OBSERVATIONS BASED UPON APPROXIMATELY 5000 PATIENTS OVER A PERIOD OF SIX YEARS.

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THE blood sedimentation test is one of the newer laboratory procedures, striving for a place as a valuable diagnostic aid and prognostic index in infectious and other destructive diseases. It has been studied extensively in two fields of medicine, in pulmonary tuberculosis and gynecology. In these fields it has been accepted by many as a valuable addition to the armamentarium of the physician and as a more reliable source of information than some of the usually accepted procedures on which he customarily bases his judgment. Its importance as a routine procedure in general medicine and especially in office and dispensary practice has, however, received little if any consideration, and it is the purpose of this paper to describe some of its possibilities.

This paper is based on experience with the sedimentation test acquired through intensive study in hospital, dispensary, and office practice during the past 6 years. What I wish to present at the

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present time is a broad outline of this experience, based upon personal observations on more than 5000 patients, covering practically every common disease encountered in the practice of "internal medicine."

It is not within the scope of this discussion to consider the various hypotheses that have been suggested to explain the phenomenon of blood sedimentation. It is safe to say, however, that out of a host of explanations, whether in terms of autoagglutination, of electrophysical reaction, of increased fibrinogen content of blood plasma, or of a specific something (ferment) in the plasma, not one is generally accepted.

However, evidence is accumulating to show that essentially the sedimentation phenomenon depends upon the amount of cellular destruction going on in the body. As the blood circulates from part to part it carries away products of tissue destruction, which alter its stability. In healthy persons, as a result of the wear and tear of everyday life, a certain amount of tissue destruction is always taking place, and although this varies from day to day it remains within limits considered normal. Even this relatively small amount of tissue destruction is registered by the sedimentation test. This was clearly shown by Greisheimer,¹ who made 174 repeated observations on a group of 31 healthy men and women and observed that the sedimentation rate varied from week to week in the same individual, but always within normal limits.

Should the amount of tissue destruction pass beyond the normal, then the stability of the blood is seriously disturbed and the red blood cells settle out quickly from the plasma. All the observations recorded in recent literature emphasize this important fact: that regardless of the disease present, whether it be active pulmonary tuberculosis, malignancy, pelvic inflammatory disease, and acute infections such as typhoid fever, or any disease in which tissue destruction is going on at a greater pace than normal, the rapidity of settling of the red blood cells is in direct proportion to the severity of the disease.

It is evident, therefore, that the sedimentation reaction portrays a disturbed physiology of the blood resulting from a destructive process, and should be looked upon as one of the fundamental phenomena occurring during disease and regarded as an indication and measure of pathologic activity in the same sense as fever or leukocytosis.

Technique. The 1 cc. Cutler graphic technique was followed throughout. This technique is very simple and can be carried out by the physician in his office without difficulty.² The essential features are as follows:

Specially designed sedimentation tubes of 1 cc. capacity are used, graduated into 50 mm. divisions, with 0 at the 1 cc. level; each millimeter indicating 0.02 of 1 cc. One-tenth of 1 cc. of a

3 per cent sodium citrate solution and 0.9 cc. of blood, obtained by puncture of a suitable vein, are gently mixed in a 2 cc. syringe and poured into the sedimentation tube. The position of the sedimenting column of erythrocytes is determined every 5 minutes for 1 hour (Fig. 1). The observations are recorded on charts that have been designed for the purpose, on which the horizontal lines represent the divisions on the tube and the vertical lines the intervals of time. Graphs are then constructed, which not only show the position of

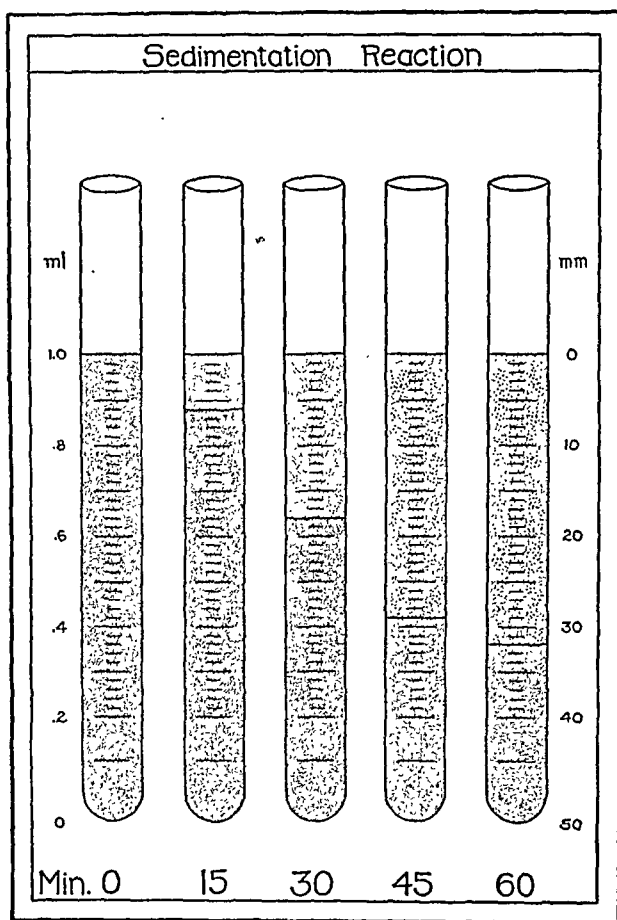


FIG. 1.—Blood sedimentation at different time intervals in a patient with rapid settling of the red blood cells (pelvic inflammatory disease.)

the sedimenting column of erythrocytes at any period of time during the first hour, but also portray the changes in velocity that occur during the process of sedimentation (Fig. 2).

Four distinct graphs are recognized, a horizontal line, a diagonal line, a diagonal curve, and a vertical curve. Of these, the horizontal line alone is normal, the other three graphs are always abnormal findings and always indicate different degrees of the intensity of the

NOTE.—The sedimentation tubes may be obtained from Arthur H. Thomas Co., Philadelphia, the charts from John Hartenstine, Norristown.

destructive process. For greater detail the reader is referred to previous communications.^{3,4}

Test Studied Under Three Headings. With this introduction let us see what the sedimentation test has to offer the busy physician when used as a routine procedure in everyday practice. It seems best, in order to avoid confusion, to discuss the test under three headings: First, its diagnostic value; second, its value in prognosis and as a therapeutic guide, and third, its limitations.

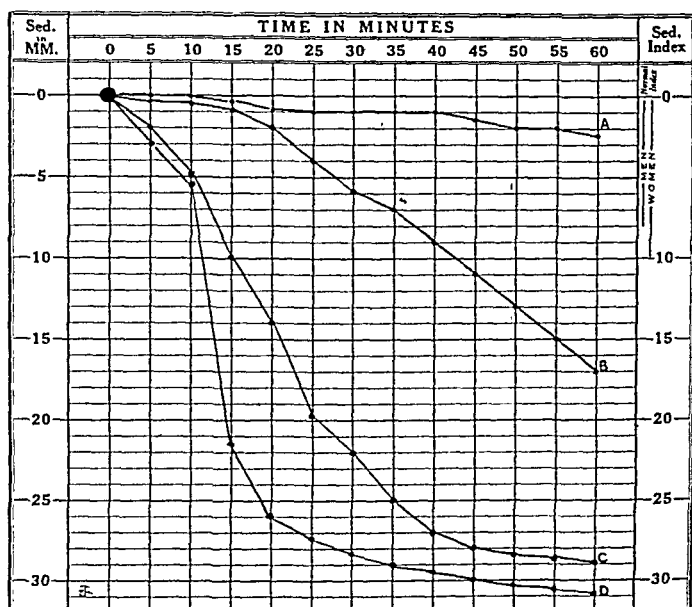


FIG. 2.—Typical graphs of blood sedimentation. A, horizontal line; B, diagonal line; C, diagonal curve; D, vertical curve. Of these the horizontal line alone is normal; the other graphs are always abnormal and indicate different degrees of the severity of the disease.

The Diagnostic Value of the Sedimentation Test. The sedimentation test is nonspecific and is not a procedure for diagnosing any particular disease (Fig. 3), but rather as a general symptom like fever and leukocytosis. As such, it serves as a valuable diagnostic aid in two ways: First, as a *lead* in diagnosis, indicating the presence of noteworthy disease, not infrequently before it is manifest clinically; and second, as a *measure* of the intensity of the disease process, often more accurately than the more commonly accepted procedures.

The sedimentation test is perhaps most useful as a diagnostic lead. A careful review of a reasonable number of records in any well conducted dispensary or office will readily convince one of the value of some simple laboratory procedure than can by a single determination indicate the presence of serious disease and distinguish the seriously ill from the patient with symptoms of minor

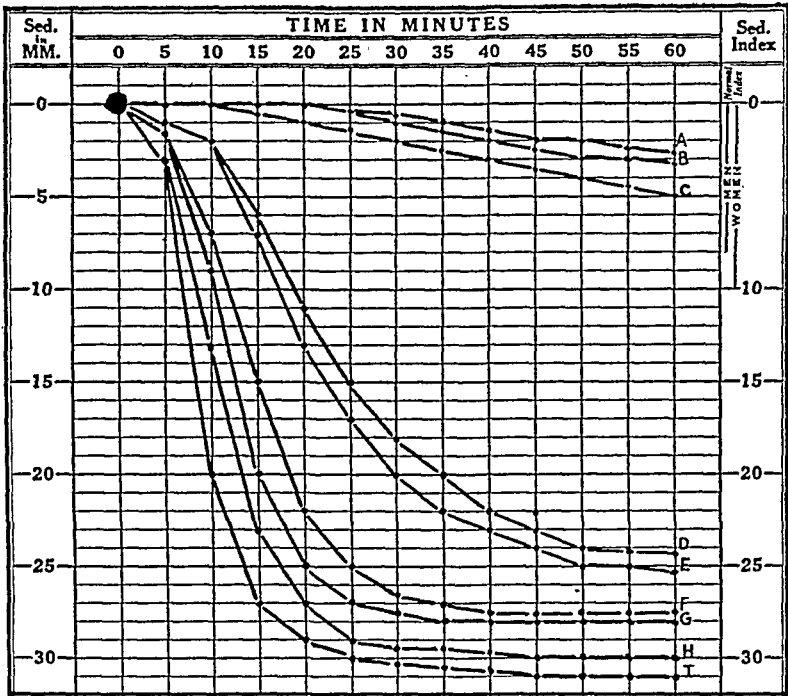


FIG. 3.—Nonspecificity of blood sedimentation test. Almost identical graphs are obtained in widely different diseases. *D*, pulmonary tuberculosis; *E*, bronchiectasis; *F*, lobar pneumonia; *G*, chronic bronchopneumonia; *H*, lung abscess; *I*, carcinoma of lung; *A*, *B* and *C* show indifference of test to pathologic conditions of noninfectious nature. The patients suffered with asthma, mitral stenosis and chronic sinusitis respectively.

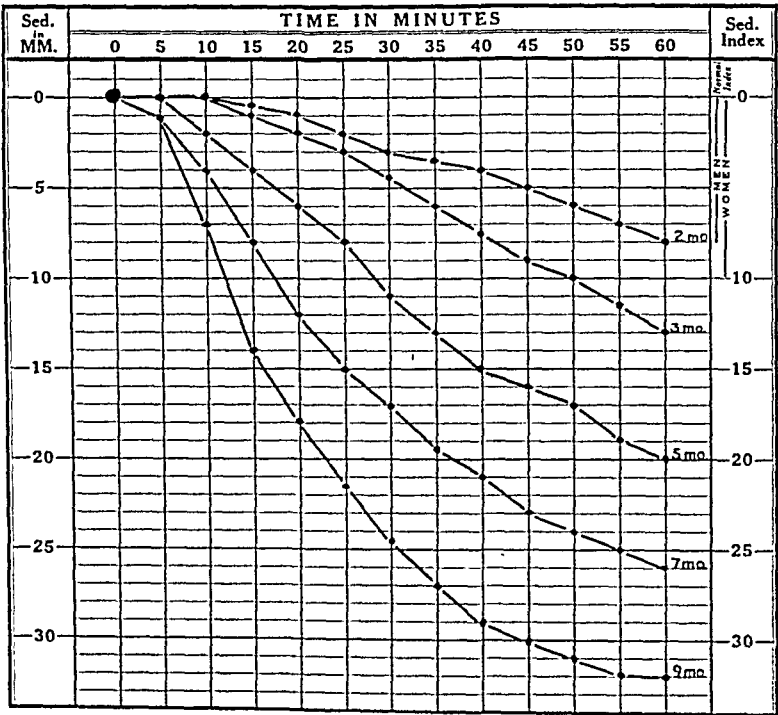


FIG. 4.—Blood sedimentation during pregnancy.

significance. Such a test would undoubtedly be of inestimable value in helping the physician arrive at an accurate diagnosis earlier and in a larger number of patients than is now possible.

In the sedimentation test we have just such a procedure. Increased settling of red blood cells, as far as we know today, occurs when there is increased destruction of tissue and, therefore, rapid sedimentation demands explanation in terms of disease and should never be disregarded. Pregnancy is the only physiologic process that is accompanied by rapid sedimentation (Fig. 4).

In a series of more than 1000 cases observed consecutively at the Henry Phipps Institute, 328 patients were diagnosed either as apparently healthy or suffering from some trivial and transient symptoms of slight pathologic importance. The diagnosis was based upon careful history and physical examination, with the usual observations as to pulse, temperature and weight. Of this number 177 (54 per cent) had a definitely abnormal sedimentation rate for which no satisfactory explanation could be given by the examining physician. When these patients, however, were subjected to routine Roentgen ray examinations of the chest, Wassermann tests, nose and throat examinations, and the women to routine gynecologic examinations, the abnormal sedimentation test no longer remained a mystery. In 96, basal infiltration of the lungs of varying extent and nontuberculous in character were found by Roentgen ray. In 32 the Roentgen ray revealed latent tuberculosis involving the apices. Positive Wassermann and Kahn reactions were found in 35. In 5 women the gynecologist made a diagnosis of pelvic inflammatory disease and recommended operation. In 1 carcinoma of the lung was suspected because of Roentgen ray findings. In 8 no definite pathology could be demonstrated but there was sufficient reason to warrant holding these patients for further observation. Thus in most of these cases the significance of the abnormal sedimentation rates was explained by the final diagnoses. These patients had either trivial symptoms or no symptoms at all. In every instance a careful physical examination by a competent physician was negative and a tentative diagnosis was made of "apparently healthy." This is particularly striking in the group of patients with significant Roentgen ray findings in the lungs, for the physicians who made the physical examinations of the chest were especially trained to recognize the early signs of disease and might properly be called "chest specialists."

The abnormal sedimentation rate in these patients undoubtedly served as a diagnostic lead, clearly indicating that in spite of negative signs and the absence of symptoms the patient was not healthy but harbored some serious ailment. If these patients had not been subjected to a painstaking search, no satisfactory explanation could have been advanced for the abnormal sedimentation and superficial criticism would have branded the test as "unreliable."

The following are typical specific instances in which the sedimentation test was or might have been of definite help as a diagnostic lead:

A woman, who was studied in different hospitals, had gall bladder symptoms and was then diagnosed as neurasthenic. Her sedimentation was active. An operation revealed carcinoma of the head of the pancreas.

A woman, with loss of weight, was told she had cancer. Her sedimentation was normal. An operation showed adherent gall bladder, and was followed by complete recovery.

A woman, with suppurative bronchitis, had had a diagnosis of nervous cough, which was contraindicated by an abnormal sedimentation rate.

A woman, with vague symptoms and a family history of tuberculosis, was apparently in good health and told to go to work. Her sedimentation rate was abnormal. She gave a positive Wassermann reaction.

Classifying the different diseases studied according to whether or not they cause increased settling of the red blood cells, we can group them under three headings.

TABLE 1.—DISEASES GROUPED ACCORDING TO SEDIMENTATION RATES.

With an Abnormal Sedimentation Rate.

1. Chronic infectious diseases, such as tuberculosis and syphilis.
2. Acute infectious diseases, such as pneumonia, septicemia, acute endocarditis, the exanthemata and acute bronchitis.
3. Malignancy.
4. Localized suppurations, such as pelvic inflammatory disease, suppurative mastoiditis, suppurative sinusitis, empyema of the gall bladder, bronchiectasis.
5. Acute intoxications, such as lead and arsenic poisoning.
6. Certain endocrine disturbances, such as thyroid toxicosis.

Influencing the Sedimentation Rate Very Little If At All.

1. Simple catarrhal inflammations, such as acute catarrhal appendicitis, simple rhinitis and colitis.
2. Chronic ulcerations of small extent, such as gastric or duodenal ulcer.

Not Influencing the Sedimentation Rate.

1. Functional diseases, such as the various neuroses, and neurasthenia.
2. Certain nervous diseases, such as dementia precox.
3. Focal infections, such as abscessed teeth, diseased tonsils and chronic sinusitis.
4. Metabolic diseases, such as uncomplicated diabetes and essential hypertension.
5. Allergic diseases, such as asthma and hay fever.
6. Most skin diseases.
7. Simple growths, such as fibroma, lipoma and fibromyoma.
8. Simple cysts.
9. Chronic valvular disease of the heart.

Rapid sedimentation, in other words, is found only in infectious disease and malignancy.

It must be clearly understood that a normal sedimentation reaction does not rule out serious disease. For instance, patients may harbor advanced tuberculosis and still have a normal sedimentation

rate. In such cases the normal reading indicates that the tuberculosis is not active, or at least there is not sufficient tissue destruction to cause increased settling of the red blood cells.

To state the same thing in another way—a normal sedimentation reaction indicates one of two things, either health or the existence of destructive disease, not sufficiently active to disturb the natural stability of the blood; an increased sedimentation reaction is always abnormal, and except in pregnancy indicates the presence of disease.

We have then in the sedimentation test a sensitive method for detecting serious disease as soon as it becomes sufficiently active to disturb the stability of the blood.

The Value of the Sedimentation Test as a Prognostic and Therapeutic Guide. The second use to which the test readily lends itself in diagnosis is its ability to evaluate in definite terms the degree of constitutional disturbance produced by the pathologic process. No diagnosis of any disease can be said to be complete without such knowledge and the skillful physician employs every aid of his profession to obtain this knowledge. It is only after an accurate and considerate estimation of the intensity of the disease process that intelligent treatment can be planned. Its importance to the welfare of the patient from a practical sense can hardly be overstated.

The ability of the sedimentation test to supply this information more accurately than most of our usually accepted procedures, such as temperature curve and pulse rate, blood count, or physical signs and symptoms, was one of its first characteristics to be recognized clinically and wide use has been made of it in tuberculosis and gynecology, in the former to indicate the activity of the tuberculous process and in the latter the safe time for operation in pelvic inflammatory disease. This aspect, its usefulness as a quantitative index, has been emphasized in many excellent contributions to the literature on the subject.

As a measure of constitutional disturbance the sedimentation test may clearly be of great value to everyday clinical practice, not only in diagnosis but also in prognosis, and as a guide to treatment. The changes in sedimentation rate parallel the severity of the disease, becoming more rapid as the disease becomes worse and slowing down to normal as the condition of the patient improves.

The graphs of subsequent sedimentation findings recorded upon the original chart is a dramatic and convincing indication of the progress of the disease in terms of constitutional disturbance, unequalled by any existing clinical or laboratory method for its accuracy and simplicity. It is not subject to psychologic influences or to the promises of a well-meaning physician or pharmaceutical house; if the treatment has no direct effect upon the disease, sedimentation will continue rapid. At times it may even increase in rapidity in the face of apparent symptomatic improvement and well-being.

Clinical Examples.—CASE 1.—A most striking example was observed in J. R., aged 67 years, who was first seen on December 3, 1929. One month later a diagnosis of carcinoma of the right bronchus was established through biopsy. The patient died 9 months later and had clinical manifestations of metastasis several months before death. About 6 months before he died he seemed to have improved clinically to such an extent that the family and the patient became unusually hopeful. His symptoms of cough and expectoration became less, pain was less marked and his strength improved. He even gained a few pounds in weight. As a coincidence his treatment at that time consisted of 5 cc. of a 5 per cent solution of calcium chlorid, given intravenously twice weekly, in addition to the usual supportive measures. The family was convinced that the patient was getting better and that the improvement was due to the intravenous medication. As can be seen from the graphs C and D (Fig. 5) sedimenta-

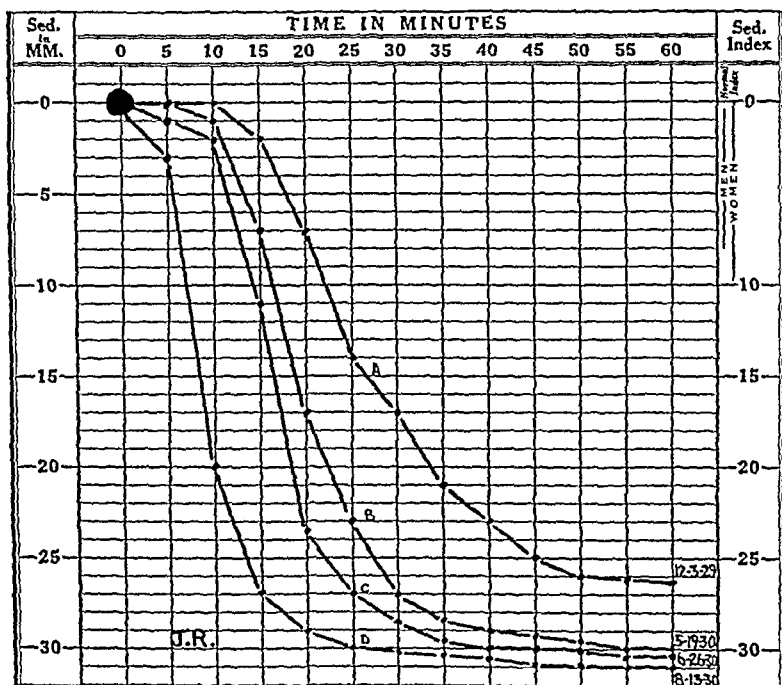


FIG. 5.—Blood sedimentation in fatal carcinoma of the lung.

tion during this period of symptomatic improvement became more rapid and continued to increase in rapidity until death. The sedimentation was not influenced by mental phenomena but remained a true guide to the severity of the malignant process and prevented the indulgence of false hopes.

A few typical examples and the accompanying figures further illustrate the usefulness of the test in prognosis and in guiding treatment.

CASE 2.—S. S., aged 23 years, was admitted to the Northern Liberties Hospital on December 19, 1929, with acute pulmonary tuberculosis involving the right upper lobe and complicated by severe hemoptysis. Artificial pneumothorax was instituted, December 21, and the patient responded well. He was discharged in good condition and practically free of symptoms

thirty days later, to continue his pneumothorax treatments in the clinic. His recovery has been uneventful and at the present time he is pursuing an active life. Fig. 6 depicts the daily variations in temperature during his

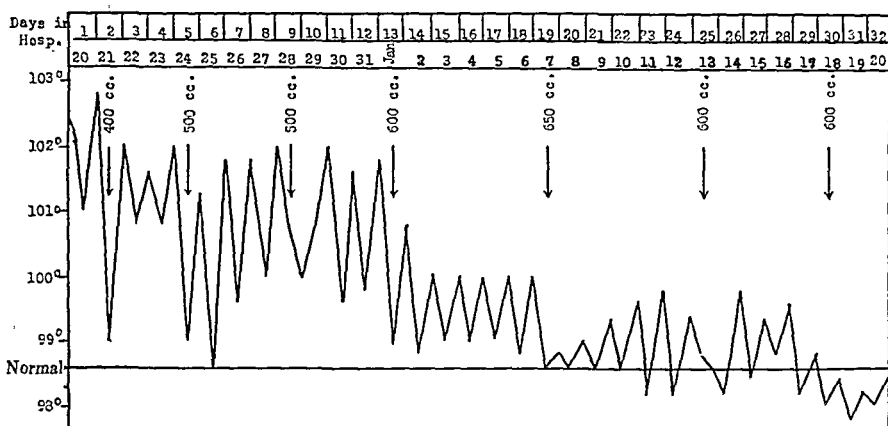


FIG. 6.—Daily temperature curve in a case of acute tuberculosis treated by artificial pneumothorax (indicated by arrow).

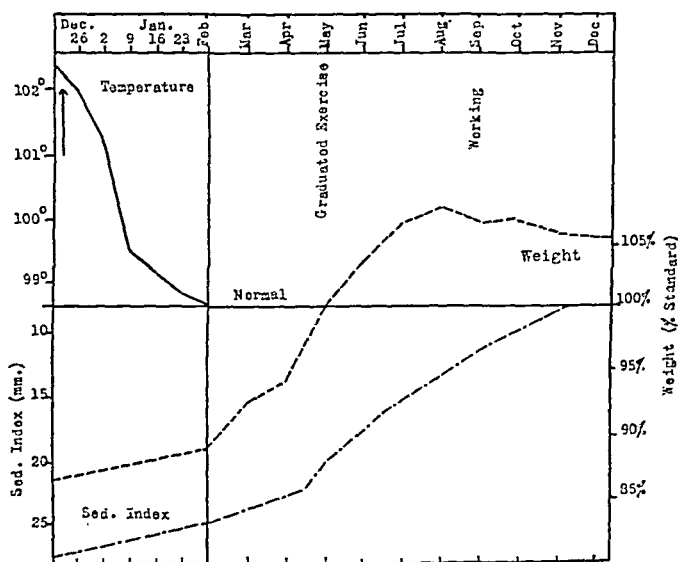


FIG. 7.—Clinical course during the first year of treatment by artificial pneumothorax illustrating the relative rapidity with which the temperature, weight and sedimentation rate returned to normal. The temperature as a representative symptom of toxemia was the first to subside. The sedimentation rate, on the other hand, did not recover until 9 months after the temperature and other signs of toxemia were absent. The vertical line denotes a change in scale from weeks to months. (Same patient as in Fig. 6.)

stay in the hospital. Fig. 7 illustrates the clinical course during the first year that the patient had been under observation and indicates the relative rapidity with which the temperature, weight and sedimentation rate returned to normal.

The temperature as a representative symptom of toxemia was the first to subside. The sedimentation rate, on the other hand, did not recover until 9 months after the temperature was normal and the signs of toxemia absent. It was the last objective observation to return to normal and for months was the only indication of the pathologic state of the compressed lung.

Fig. 8 illustrates the course of the sedimentation graph observed during the first year of treatment as recorded on one chart and shows what an excellent method we have here for visualizing steady improvement in favorable cases. The shaded area of the chart indicates the sedimentation graphs obtained during the absence of clinical signs and symptoms, at a time when something was desperately needed to indicate the true state of

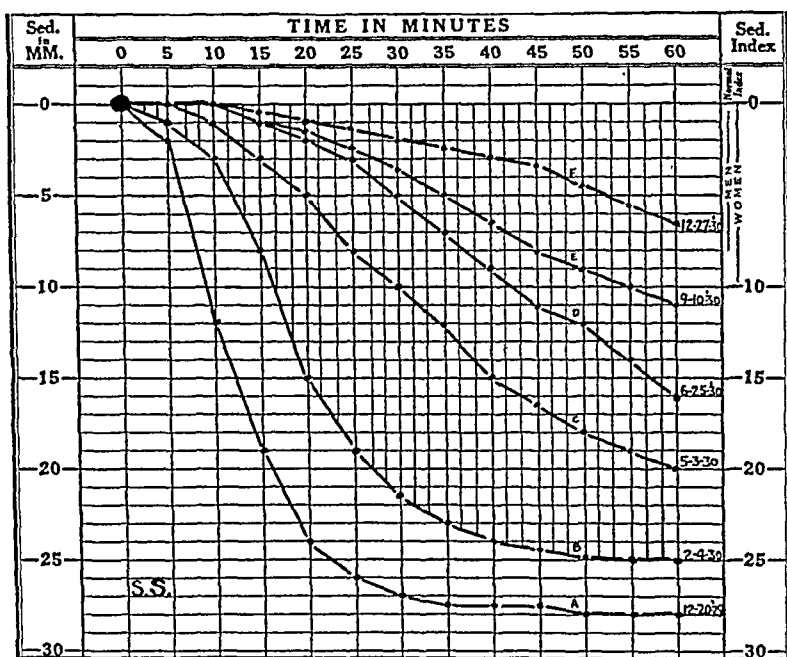


FIG. 8.—Sedimentation graphs obtained during first year of treatment by artificial pneumothorax. The shaded area indicates the sedimentation graphs obtained during the absence of clinical signs and symptoms. (Same patient as in Figs. 6 and 7.)

affairs in the compressed lung. Without the sedimentation test the clinical management of this case would have been much more difficult.

When the disease is not responding to treatment the sedimentation test will either remain fixed or increase in rapidity.

CASE 3.—F. P., aged 24 years, first came under observation for advanced pulmonary tuberculosis involving the left lung in February, 1930, when artificial pneumothorax was started. She has been under treatment ever since. Unfortunately the cavities in the left lung can be compressed very slowly and with great difficulty because of the adhesions and, although clinically she is comfortable, there has been little if any improvement in the sedimentation rate over a period of 1 year. Fig. 9 illustrates some of the graphs observed during this period in this patient, and is very convincing proof of the lack of actual improvement in the lung.

Fig. 10 illustrates the steady increase in rapidity of sedimentation in a patient with bilateral tuberculosis who at first responded remarkably well to artificial pneumothorax and then suffered a spread in the right or "good" lung. The spread was rather extensive, and at first gave no warning clinical signs or symptoms. It was only because of the unexplained increases in the rapidity of the sedimentation rate that the true state of affairs was

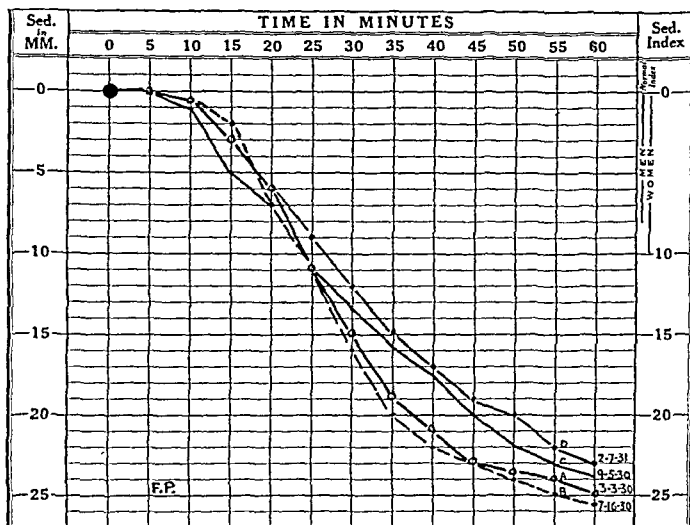


FIG. 9.—Sedimentation graphs obtained during the course of chronic pulmonary tuberculosis treated by artificial pneumothorax but with little or no improvement.

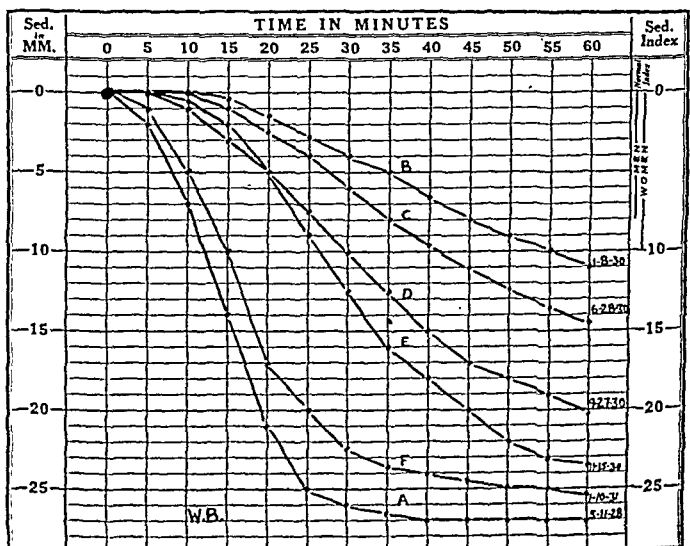


FIG. 10.—Sedimentation graphs obtained during the course of chronic pulmonary tuberculosis treated by artificial pneumothorax with spread in the untreated or "good" lung. A, before treatment was started; B, nineteen months later (patient free of symptoms and able to do a full day's work); C, D, E, F, increased sedimentation accompanied by extensive spread in right or "good" lung with cavity formation. Patient ordered back to bed at D.

quickly recognized and the patient ordered back to bed. Even to this day, although we know that there is advanced disease in the "good" lung, as revealed by Roentgen ray and fluoroscopic study, one can detect very few if any definite physical signs. The patient is free of fever and cough and has only slight expectoration in the morning. He is overweight and feels well in every respect. The unexplained increase in sedimentation rate, determined as part of routine practice in the management of such cases, serves, like a storm signal in a calm, as a warning that trouble has begun, and that it is no less real because it is not yet visible.

Other striking examples of the usefulness of the sedimentation test as a check upon therapeutic measures are shown in the accompanying illustrations. Some of the cases have been described in detail and others are sufficiently explained by the legends. Space forbids further discussion of interesting examples. The reader will find that the literature is rich in contributions on this phase of the subject, but best of all he can find his own examples through clinical trial at the bedside.

Limitations of the Sedimentation Test. The author is well aware that much criticism will be directed against this test, if for no other reason than because the claims made for it are of such fundamental importance as to challenge the imagination. No doubt some will argue that if what is claimed is true then all that one will have to do in the future to know anything desired about the state of the patient is to perform a sedimentation test. On the other hand, others will see no value in it at all. They will argue that the sedimentation test is merely another addition to the laboratory playhouse—interesting but not essential. If the physician will study his patient carefully and employ every method at his command at present, he will not need this new trick to tell him if his patient is ill, what to do for him or what the outcome will be.

These criticisms are heard many times. One can only reconcile oneself with the observation that it is in the nature of things for anything new to be challenged. Anything that stirs our stagnation and forces us to change our habits of thought and action is almost sure to be looked upon by some with suspicion and even regarded as an offence.

The sedimentation test is not a substitute for any existing clinical or laboratory procedure. On the contrary, it is complementary to them, and therefore essential, because it fills certain important gaps left by current methods. Although at first it may seem a luxury, repeated use at the bedside will soon establish it as a real necessity.

The sedimentation test will not make a good doctor out of a poor one, but it will undoubtedly make a keener and better physician out of a good one. The physician and not the test must determine the nature of the pathologic condition it points out to him. The test has served its purpose in diagnosis when it has indicated the existence of disease and thus warned the physician to make an unremitting search for the source of the disturbance. Once the diagnosis has been established the rate of sedimentation becomes a

measure of the intensity of the disease, more accurately than our commonly accepted procedures, and serves as a record of the response to treatment. It is obvious, therefore, that the sedimentation test has a field of usefulness of its own, not readily covered by existing laboratory and clinical methods. When we learn to look upon the increased rapidity of the settling of red blood cells as a measure of tissue destruction regardless of etiology, we shall have begun properly to interpret the test. We shall then begin to see the possibilities of its routine use in office, hospital and clinic.

The sedimentation test has certain real limitations which should be borne in mind: (1) It does not give a diagnosis of a specific disease. Neither does fever, nor leukocytosis. (2) A normal sedimentation is not conclusive evidence that there is no disease, but it does show that disease, if present, is producing very little if any constitutional disturbance. (3) Abnormal sedimentation reveals pathologic processes that cause tissue destruction, but these include the infectious diseases and malignancy. (4) Sedimentation is abnormally rapid with pregnancy after the third month. (5) The test is not infallible. I have seen a few instances and some have been brought to my attention of a normal sedimentation rate with clinically active disease. These cases are very rare and the reasons for them obscure. I recall only 5 in over 5000 observations. When we know more about the mechanism involved these exceptions may take on a meaning of their own. It is also true that not every abnormal sedimentation can always be explained in terms of disease, but such cases should be regarded as suspicious until proved otherwise.

Summary. The blood sedimentation test has been studied in hospital, office and dispensary practice during the past 6 years with more than 5000 patients. The test was found to be of distinct diagnostic and prognostic value in diseases characterized by disturbed stability of the blood. A list of such diseases has been drawn up, but consideration of the value of the test in any given disease has been reserved for separate communications. The present purpose is to describe and illustrate the fundamental characters of the sedimentation test in disease in general.

In diagnosis the test has two values, first as a diagnostic *lead* and the second as a diagnostic *gauge*. As a diagnostic lead it indicates the presence of serious disease, not infrequently before the disease can be recognized by the usual clinical and laboratory methods. As a gauge of the constitutional disturbance produced by the pathologic process, it indicates the intensity of the disease and thus, like fever or pulse rate or blood count, but more exactly, helps to complete the diagnosis in a qualitative sense.

As a prognostic index and, similarly, as a guide in treatment, the rate of sedimentation has been shown to be a more accurate and reliable reflection of the real condition of the patient than our usually accepted procedures. It invariably becomes more rapid as the

disease progresses, and approaches stability only as the physical condition returns to normal. It is not influenced by psychologic factors and may be the only warning of disaster among promising clinical signs, such as gain in weight and the absence or subsidence of symptoms. In this way it is often the only, or the most accurate, evidence of favorable, or of unfavorable, response to treatment.

The test is very simple to perform and to interpret and is inexpensive. It is a clinical procedure and can be carried out in the office, in the dispensary or at the bedside. The complete result is available within an hour and in case of necessity the sedimentation test will give valuable information within the first half hour.

Its greatest field of usefulness should be in office and dispensary practice, especially in the latter, where large numbers of patients must often be seen in short periods of time and by men seeking experience. Properly interpreted and used with an open mind, the test should in time become one of the most widely used tests in clinical medicine.

Its practical value in any given disease is best studied as a separate problem and such studies should be undertaken in large numbers so that sufficient data become available in a short period of time. Only in this way will lingering doubts be removed and the sedimentation test firmly established as a valuable addition to the equipment of the physician.

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PATHOLOGIC CHANGES OCCURRING IN POLYMORPHONUCLEAR LEUKOCYTES DURING THE PROGRESS OF INFECTIONS.

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THE response of the blood-forming organs to infections is influenced by the type of the invading organism and the intensity and extent of the infection. Ordinarily, pathogenic organisms call

forth a leukocytosis and a polynucleosis, while certain forms of obscure infection are followed by a lymphoid or monocytic response. In some infections, notably subacute bacterial endocarditis, macrophages may appear in the peripheral blood. In trichinosis the main reaction is shared by the eosinophils. Leukocytosis and polynucleosis may be absent in infectious conditions which are more or less severe. In such instances the ordinary blood examination may be insufficient and misleading, while attention to certain other details of the individual cell, such as nuclear and cytoplasmic changes, may indicate the presence of an underlying bacterial infection.

In addition to the value of the white and differential count, this paper is intended to show the significance of the nuclear and cytoplasmic changes in the granulocytes which occur in certain infections because these have a diagnostic and prognostic importance. Realizing the need for more detailed methods of examination, Arneth,¹ in 1904, proposed a subdivision of the leukocytes into various types. He showed that the main response to infection occurred in granulocytes which had one or two lobules to the nucleus. Kothe² and Türk³ suggested further simplification of the method of counting polymorphonuclear cells by dividing them into lobulated and nonlobulated cells. The value of this modification of the Arneth count has been emphasized by Pons and Krumbhaar,⁴ who divided the polymorphonuclear leukocytes into segmented (or older cells) and nonsegmented (or younger cells). Recently Farley⁵ introduced filament and nonfilament count, corresponding to the segmented and nonsegmented polymorphonuclear cells. Schilling modified the Arneth method and classified the polymorphonuclear cells into three groups: (1) *Young cells, or metamyelocytes*, which are not present in normal blood and which usually have a short, broad, reticulated nucleus; (2) *the staff or band form*, which shows a thinner nucleus, somewhat irregular in shape; (3) *the segmented polymorphonuclear cell*, in which the nucleus is lobulated and the lobules are joined to one another by a definitely formed thread. It is often difficult to distinguish between the young cells and the band form, and it would not detract from the value of the hemogram to combine the two types of cells, according to the methods of Kothe or of Pons and Krumbhaar.

The diagnostic importance of the increase of the nonsegmented polymorphonuclear cells cannot be overestimated. An increase of these cells or shift to the left (toward the staff type) in a series of blood examinations usually is indicative of severe infection. The greater the number of nonlobulated cells above the normal (average normal is 5), the more extreme is the degree of infection.

Previous observers have noted cytoplasmic as well as nuclear changes in the granulocytes. Such cytoplasmic changes are large, irregular, basophilic alterations of neutrophilic granules. Cesaris-

Demel⁷ (1908), employing supravital stains in studying the leukocytes, reported the finding of marked albuminoid and fatty granular changes. Schleip⁸ noticed denser granules in the polymorphonuclear cells in leukocytosis. We are indebted to Türk³ for the first complete description of the "toxic degenerative" changes in the granulocytes during severe infections. Naegeli,⁹ Alder¹⁰ and, especially, Gloor¹¹ paid particular attention to the prognostic importance of the granulocytes with "toxic" granules. Special stains for the identification of these granules were devised by Freyfeld¹² and Mommsen;¹³ the latter investigator showed that blood smears stained with Giemsa (diluted with a buffered solution of pH 5.4) colored normal granules rather weakly in contrast to the "toxic" granules. More recently Varga¹⁴ called attention to the presence of two types of granules—large in the febrile stage and small in the convalescent stage. This writer found no direct relationship between the Schilling hemogram and "toxic" granules. These granules are present with either hyperleukocytosis or leukopenia. In contradistinction to the theory that "toxic" granules are the result of histologic degenerative change (Schilling¹⁵) or to a toxic effect associated with suppuration (Naegeli,⁹ Gloor¹¹), Barta¹⁷ has lately suggested that they are phagocytosed particles.

Methods of Demonstrating Toxic Degenerative Cells. Inasmuch as the value of any laboratory method depends directly upon its accuracy and its simplicity, we have, after trying various stains and methods, finally used our routine Jenner-Giemsa* stain, maintaining the water at a pH of 6.4 to 7. This method consumes only 15 minutes and gives blood pictures which are adapted to minute study of the normal as well as the pathologic changes in the individual cell.

Control smears from normal blood should always be made. This is done by using the outer third of the slide for the normal smear and making it at an angle so as to distinguish it from the patient's blood on the same glass slide. In this manner the staining quality of the patient's granulocytes can be readily compared with the normal.

Degenerative Cytoplasmic Changes. The *normal* polymorphonuclear neutrophil, when stained with the Wright or preferably with the Jenner-Giemsa stain, is usually a round cell, more than twice the size of a red cell. The cytoplasm shows a pinkish tint, and the nucleus is of a purplish-violet color, its outline being sharply defined. (Fig. 1.)

* Blood smears are covered with Jenner's stain for 1 minute, and then diluted with distilled water at a pH of 6.4 to 7 for 3 minutes. Distilled water can be brought to proper pH by adding 3 cc. of $N/15$ Na_2HPO_4 to 1000 cc. of distilled water. The slide is then tilted to remove diluted Jenner, washed once with buffer solution and Giemsa solution added (1 drop to 1 cc. buffer solution) for 10 minutes. The slide is then washed and dried. Wright stain may also be used with the same buffer solution to identify "toxic" granules.

The *abnormal or degenerative* polymorphonuclear neutrophil, on the other hand, presents certain striking histologic changes. The cell outline has a tendency to be irregular, and at times presents a moth-eaten appearance. The cells also vary in size in a manner analogous to anisocytosis of the red blood cells. (Fig. 2.) There are found in a few cells projections of clear bluish cytoplasm suggestive of pseudopodia. The fine neutrophilic granules are replaced by large, dark, irregular, basophilic granules which may fill the entire cell. (Fig. 3.) These granules may be free from or may be associated with changes in the cytoplasm, such as the presence of irregular bluish clumps (Doehle bodies) or a diffuse bluish cytoplasm found in myeloblasts. Further evidence of degeneration is shown in the presence of vacuoles, sometimes few in number and at times occupying most of the cytoplasmic area. These vacuoles may be present in a cell without the accompanying basophilic granular changes. It must be emphasized that the pathologic changes in the cytoplasm of the degenerative cells were found to be equally great in the younger and immature polymorphonuclear leukocyte as in the mature segmented forms, *i. e.*, they were not dependent upon the age of the cell.

Nuclear changes such as were described by Arneth and, later, by Schilling, were noted by us. These alterations are usually indicative of active regeneration; they can also occur in noninfectious conditions, such as hemorrhage, excessive exercise and following surgical operations.

Modified Hemogram. The counting and differentiating of these cells may be simplified by the use of a modification of the Schilling hemogram. (Table I.)

TABLE 1.—MODIFIED HEMOGRAM.

PATIENT: Baby S.	WARD X	DATE: 1-10-31
DIAGNOSIS: Pneumonia.		
HEMOGLOBIN: 65 per cent		
RED CELLS: 5,010,000		
PLATELETS: 320,100		
LEUKOCYTES: 5100		
DIFFERENTIAL COUNT:	Total, per cent.	Normal. "Toxic."
Polymorphonuclears, nonsegmented . . .	73	0 73
Polymorphonuclears, segmented . . .	15	0 15
Polymorphonuclear eosinophils . . .	0	Degenerative index:
Polymorphonuclear basophils . . .	0	(88 ÷ 88) — 100
Lymphocytes . . .	15	Clinical data:
Monocytes . . .	13	Bronchopneumonia, 11th
OTHER CELLS:		day; temperature, 105° F.
Myelocyte neutrophils . . .	3	
Myeloblasts . . .	6	

It became obvious at the outset that the degenerated cells are associated with infections. A single determination of the presence of degenerated cells, though helpful, is not sufficient. Serial observations should be made during the course of an infection. Our main purpose in using the hemogram was to obtain a quanti-

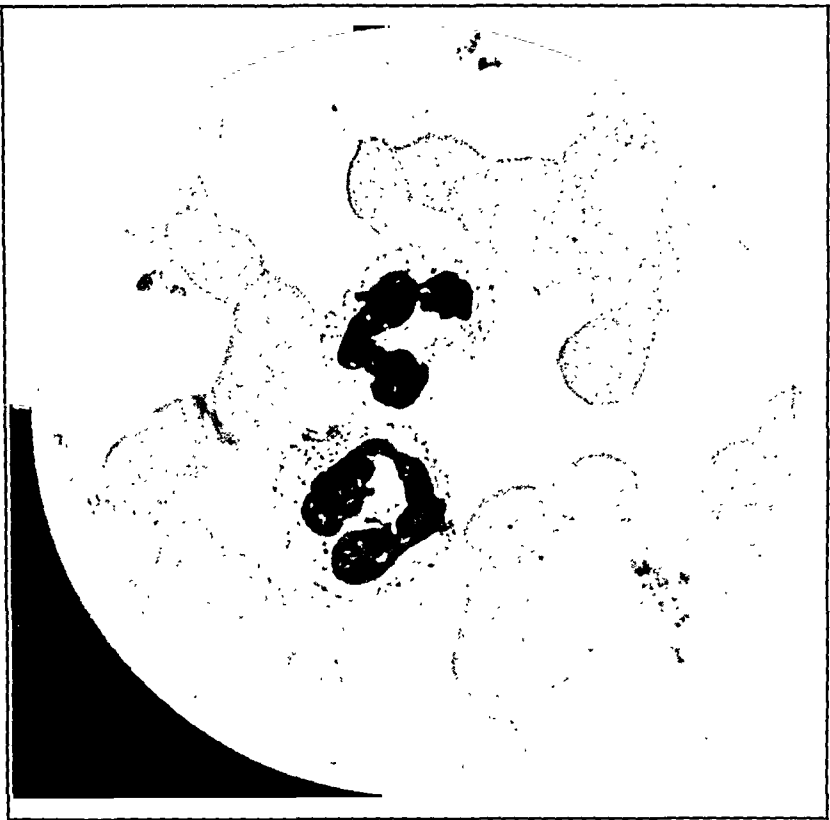


FIG. 1.—Appearance of polymorphonuclear neutrophils with Jenner-Giemsa stain in a normal control smear. Note the absence of "toxic" granules.

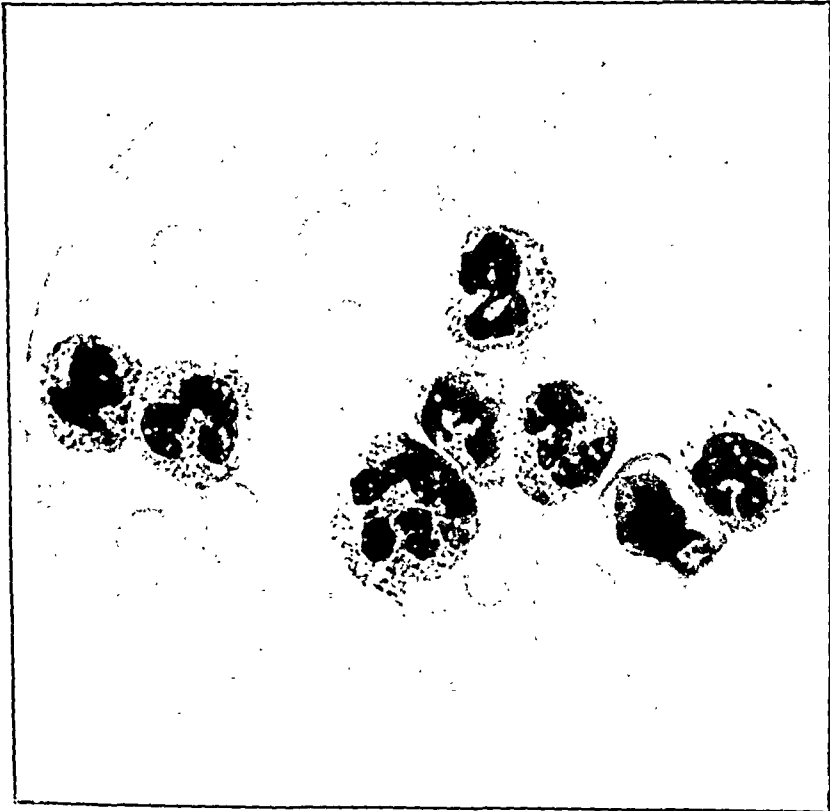


FIG. 2.—Acute lobar pneumonia (Jenner-Giemsa stain). "Toxic" granules in all segmented and nonsegmented polymorphonuclear neutrophils. Note anisocytosis of the leukocytes and also large polymorphonuclear neutrophils.



FIG. 3.—Acute lobar pneumonia, convalescent stage (Jenner-Giemsa stain). Note variations and staining intensity of "toxic" granules in the segmented and non-segmented polymorphonuclear neutrophils.

tative estimate of the number of degenerated cells. The percentage of pathologic cells may be estimated by dividing the number of degenerated polymorphonuclear leukocytes by the total number of polymorphonuclear leukocytes. This may be regarded as a *degenerative index*. Mommsen¹³ reported the variations in the number of degenerated cells in certain infections, and found a rise in the number of these "toxic" cells during the disease and a diminution during convalescence.

The study of infections with the use of the modified hemogram proved to be of practical importance. Over 100 cases showing various degrees of infection were studied. The cases studied may be divided into the following four definite groups:

1. *Normal Controls*. Numerous controls were always made in normal individuals, as a check upon the proper staining of the cells. Degenerative polymorphonuclear cells were rarely found; possibly one or two cells showed cytoplasmic changes. The degenerative index was always approximately 0. The variation of the nonsegmented polymorphonuclear neutrophil usually ranges from 1 to 10 per cent.

2. *Nonsuppurative Conditions Showing Leukocytosis*. Eight typical cases were studied. Bleeding or operation was the basic cause of a polynucleosis. Nonsegmented (or staff) cells were increased in 4 of the cases (14 to 46 per cent). Degenerative changes, however, were lacking. The total number of white blood cells varied from 9000 to 36,000. In this series we were able to verify the fact that a marked increase of nonsegmented polymorphonuclear cells may occur in conditions other than infections. This tends to emphasize the importance of recognizing degenerative changes in the cytoplasm of the polymorphonuclear leukocytes.

3. *Infections—Recovered Cases*. Interesting blood reactions were observed in this study of cases which included various infections, such as mastoiditis, appendicitis, lobar pneumonia, empyema, puerperal sepsis, etc. Certain localized infections, such as mastoiditis, appendicitis, subperiosteal abscess and similar conditions, may not be associated with either leukocytosis, polynucleosis or toxic changes unless there is an extension of the process or complications occur: then there is first an increase of the segmented polymorphonuclear cells followed by a rapid increase of the nonsegmented forms. In more severe infections, such as pneumonia or transient bacteremia, our results correspond with the findings of Mommsen,¹³ in that there is a marked increase of the polymorphonuclear cells with degenerative granules early in the infection and a complete disappearance of these cells with recovery. The degenerated index is at first rather high (21 to 93 per cent) in the first examination of patients on admission to the hospital. In all these cases there was a gradual diminution in the numbers of the degenerated cells, with complete disappearance on recovery.

TABLE 2.—ILLUSTRATIVE CASES.

Case No.	Diagnosis.	Blood culture.	Leuko- cytes.	Nonseg- mented poly- morpho- nuclears, per cent.	Seg- mented poly- morpho- nuclears, per cent.	Lympho- cytes, per cent.	Mono- cytes, per cent.	Degener- ative index.	Remarks.
1	Menorrhagia	Not done	6,400	6	54	34	6	0	Recovered
2	Splenectomy (purpura)	Not done	36,000	34	63	2	1	0	Recovered
3	Ectopic gestation	Not done	29,800	14	81	3	2	2	Recovered
4	Mastoiditis	Negative	6,200	7	46	44	3	0	Recovered
5	Appendicitis with abscess	Not done	12,200	4	79	12	5	0	Recovered
6	Pneumonia	Negative	10,000	47	42	6	5	86	Recovered
7	Empyema	Not done	26,000	29	41	19	8	100	Recovered *
8	Typhoid fever	Bacillus typhous	4,000	49	32	12	4	28	Recovered
9	Puerperal sepsis	Streptococcus (in flasks)	9,400	41	31	27	1	76	Recovered
10	Ulcerative colitis	Negative	17,400	37	17	37	9	85	Recovered *
11	Subacute bacterial endocarditis	Streptococcus viridans	17,000	49	38	8	5	10	Died
12	Subacute bacterial endocarditis	Streptococcus viridans	8,400	52	40	6	1	100	Died
13	Miliary tuberculosis	Not done	6,600	35	53	9	3	97	Died
14	Pneumonia	Pneumococcus (Type I)	11,000	68	25	6	1	95	Died
15	Pneumonia	Pneumococcus (Type II)	10,000	57	37	4	2	100	Died
16	Sepsis	Staphylococcus aureus	14,000	42	37	15	6	92	Died
17	Suppurative pyelonephritis	Bacillus coli	7,000	64	13	9	6	100	Died
18	Meningococcus sepsis	Meningococcus	27,400	52	33	6	6	20	Died
19	Diphtheritic laryngitis	Not done	60,000	61	30	4	5	100	Died
20	Malignant leukopenia	Negative	1,800	41	10	44	5	88	Died
21	Ulcerative carcinoma of uterus	Not done	4,400	34	62	2	2	95	Died

* Transfusion.

In cases of widespread infection, especially in pneumonia, the degenerative index was found to fall gradually after the crisis. In these instances the curve more nearly approximated the underlying disease than the clinical picture, temperature, pulse, etc. This was also true in a case of postabortive sepsis in which the temperature rapidly returned to normal after the spontaneous expulsion of placenta. The persistence of degenerated cells after the temperature, pulse and total white blood count have returned to normal strongly suggests that, even despite apparent clinical recovery, the underlying process is not entirely healed.

It is important to note that a high degenerative index is not necessarily accompanied by a fatal outcome. On following these cases repeatedly it was found that a persistence of a high degenerative index is usually a warning of the persistence of severe infection or deep suppuration which may require surgical intervention. An example of this is a case recently observed in one of the surgical wards, of a middle-aged man who complained of pain, of 6 days duration, in the right lower quadrant of the abdomen. After admission to the hospital the pain subsided somewhat, and palpation of the abdomen did not show rigidity or tenderness. His temperature and pulse were normal; the blood picture was approximately normal as the number of white blood cells and polymorphonuclear cells were concerned. According to the hemogram, the blood picture was as follows:

White blood cells, 9300

	Per cent.
Nonsegmented polymorphonuclear neutrophils	15
Segmented polymorphonuclear neutrophils	52
	— 67
Lymphocytes	28
Monocytes	5
Degenerated polymorphonuclear cells	2
Degenerative index ($2 \div 67$), 3	

The patient's condition improved clinically, so that surgical interference seemed unwarranted. The degenerative index, followed from day to day, ran contrary to the clinical course and, based on our past experience, the findings seemed to indicate the presence of suppuration. On the third day of admission the blood picture showed a degenerative index of 56 and showed the following:

White blood cells, 13,400

	Per cent.
Nonsegmented polymorphonuclear neutrophils	24
Segmented polymorphonuclear neutrophils	42
	— 66
Lymphocytes	29
Monocytes	5
Degenerated polymorphonuclear cells	37
Degenerated index ($37 \div 66$), 56	

On the fifth day tenderness reappeared in the right lower quadrant and an indefinite mass was distinctly felt. At this time the degen-

erative index again rose to 68. His temperature at no time was higher than 100° F. and the pulse remained normal. An abdominal exploration was made and a large retrocecal abscess was found. The day following the operation the degenerative index reached 89, and then gradually fell so that 15 days after operation, when the patient had fully recovered, only 2 per cent of the cells were found to be degenerated.

These findings should suggest the importance of additional data concerning the character of the cytoplasmic changes in the leukocytes in surgical cases and may explain some of the apparent discrepancies between blood picture and operative findings.

4. *Suppurative Conditions—Fatal Cases.* The degenerative index in all of these cases was usually high, or rapidly rose to a high percentage. The trend of the index was upward, in contrast to the trend in the recovered cases. There appeared to be more correspondence with the clinical symptoms and final course of the disease than with the number of the staff polymorphonuclears. The lowest degenerative indices were found in *Streptococcus viridans* and in meningococcus infections; it was somewhat higher in *Streptococcus hemolyticus* infections, and was highest in pneumococcus and staphylococcus infections. (Table 2.)

Many degenerative cells were found in the blood smear in a case of carcinoma. The degenerative index was high (95). At post-mortem examination an ulcerative, sloughing, infected carcinoma of the uterus was found.

The persistence of a degenerative index between 90 and 100 is of grave prognostic import and is usually followed by death.

Illustrative Cases. Two typical cases are described to show the correlation between the course of the disease and the degenerative index.

Case Reports.—CASE 1. A negro, aged 27 years, was admitted to the hospital, with a history of cough (3 days), weakness, and chilliness (1 day). The temperature was 105.4° F., and signs of pneumonia of the left lower lobe were found. On the seventh day of the disease the temperature came down by crisis. The number of white blood cells varied from 29,000 to 36,000 during the first 2 days and later was 20,000. The white blood count remained elevated long after the fever had subsided, with a sharp, fleeting rise of 1 day's duration 3 days after the crisis. (Table 2). The nonsegmented polymorphonuclear cells ranged from 61 per cent on the day of admission to 27 per cent the day of discharge. Myelocytes and myeloblasts were 8 per cent on admission and they gradually diminished, so that none were present in the blood smear the day of discharge. The degenerative index on admission was 93 and remained around 80 until the day after the critical fall of the temperature. At this time the degenerative index fell to 40. On the fourth day after the crisis, the degenerative index again rose to 97 and remained at that level for 3 days, dropping afterward toward normal.

A secondary rise in pneumonia shortly after the crisis has previously been noted by Mommsen.

TABLE 3.—S. A. PNEUMONIA.

Date, 1930.	White blood cells.	Polymorphonuclears.		Lympho- cytes.	Mono- cytes.	Degenera- tive index.
		Non- segmented.	Segmented.			
Nov. 18 . .	29,000	61	29	3	7	93
Nov. 19 . .	36,000	47	42	10	1	84
Nov. 21 . .	20,000	44	50	4	2	83
Nov. 24 . .	18,000	42	50	6	2	80
Nov. 25 . .	22,000	54	39	3	4	40
Nov. 27 . .	33,600	45	39	10	6	97
Nov. 28 . .	23,800	41	47	8	4	98
Nov. 29 . .	22,000	44	42	6	8	96
Dec. 1 . .	16,000	26	48	14	12	79
Dec. 3 . .	13,000	27	56	12	5	38*

* Discharged. The blood count on the day of discharge, showing a moderate leukocytosis, a high percentage of nonsegmented cells, as well as a degenerative index of 38, suggests that we are at times discharging patients from the hospital before the disease process is entirely healed, and indicates the necessity for an extension of the convalescent period.

In the other cases of our series we were impressed with the fact that the curve of the degenerative index may at times follow more closely the underlying pathologic process than the temperature or the ordinary white blood count. This seems most likely to occur in pneumonia. A Roentgen ray examination of the chest 3 days after the crisis showed that the left lower lobe was undergoing resolution.

CASE 2.—A woman, aged 56 years, entered the hospital complaining of fever for 8 days.

Past history: Mastectomy 12 years ago, pneumonia 3 years ago, and painful finger joints for many years. Four months ago the patient had an infected finger followed by extensive swelling, redness and tenderness of the arm, with chills, fever (106° F.), and weakness. The chills and fever subsided after 10 days, but the weakness continued. Three months ago she was seized with a severe paroxysm of pain in the back, accompanied by high fever 101° to 105° F.), profuse sweats, loss of appetite, and delirium.

Upon admission, the patient was found to be breathing rapidly; there were râles at both bases, and edema of the legs; she appeared acutely ill. The temperature mounted steadily and marked weakness and sweats continued. A week after admission there was severe pain in the legs followed by the appearance of phlebitis in the right calf. A blood culture taken on the ninth day after admission showed *Streptococcus hemolyticus*; 11 days after admission she became stuporous and died. The postmortem examination showed suppurative spondylitis and perispondylitis of the fifth lumbar and fifth sacral vertebrae, right pyosalpinx, and right femoral phlebitis.

The study of the leukocytes in this case showed that the total white blood cells remained the same throughout the course of the disease. The degenerative index on admission was 80 and rose gradually, persisting around 88 for 5 days. On the thirteenth day in the hospital all the polymorphonuclear neutrophils showed

degenerative changes; the degenerative index was 100. (Table 3.) The hemogram in the fatal cases showed, in most instances, a high degenerative index. In the cases which were followed serially the degenerative index remained high, rising toward 100 as the disease progressed to a fatal issue. It was not unusual to see a fatal result in cases with a degenerative index of 100.

TABLE 4.—C. G. STREPTOCOCCUS HEMOLYTICUS SEPSIS.

Date, 1930.	White blood cells.	Polymorphonuclears.		Lympho- cytes.	Monocytes.	Degenera- tive index.
		Non- segmented.	Segmented.			
Sept. 11 . .	19,600	38	48	11	3	80
Sept. 16 . .	18,600	55	32	10	3	88
Sept. 17 . .	16,600	57	39	3	1	83
Sept. 18 . .	20,600	53	42	3	2	88
Sept. 20 . .	16,650	72	20	5	3	87
Sept. 22 . .	21,000	54	44	2	0	100*

* Exitus.

Summary. A study of the blood in various types of infection shows marked variation in the number of leukocytes and in the number of nonsegmented and segmented polymorphonuclear cells. Reports of ordinary blood examination limited to the number of leukocytes and the percentage of polymorphonuclear neutrophilic cells may be misleading and are not helpful in formulating conclusions, either of a diagnostic or a prognostic character.

The division of the polymorphonuclears into nonsegmented and segmented polymorphonuclear neutrophils is important. The first response in infection apparently is an increase in the number of leukocytes and of the segmented cells. Then the nonsegmented cells increase rapidly. The increase of these immature cells indicates a growing activity of the bone marrow and not necessarily an infection.

Cytoplasmic granular changes in the polymorphonuclear leukocytes appear in certain infections. The changes include marked basophilia of the granules and, less frequently, vacuolization of the cytoplasm and certain cytoplasmic masses known as Doehle bodies. The basophilic, or "toxic," granules are seen only in infections—most often in bacteriemias. In streptococcus infections they occur late, particularly in subacute endocarditis; but in other conditions, especially those associated with more or less extensive suppuration (as in pneumonia) they make their appearance early and usually persist for weeks after the crisis. The cells showing "toxic" granules occur in both the segmented and nonsegmented polymorphonuclear neutrophils. The absence of "toxic" granules is suggestive of a mild or localized infection. A persistence of this condition indicates a good prognosis or the absence of complications.

The absence of "toxic" granules or degenerative changes in the cytoplasm of the polymorphonuclear leukocytes in cases of severe infection is unusual.

The degenerative index offer a prognostic guide in infectious conditions. A decrease of the degenerative index is an indication of recovery. A steady increase of the degenerative index is suggestive of either a complication or a bad prognosis. A degenerative index over 90 per cent is usually associated with a severe infection, regardless of the clinical condition of the patient and is of unfavorable significance.

Frequent observations of patients through the study of nuclear changes, such as segmentation and nonsegmentation, combined with a consideration of the cytoplasmic changes, are a most valuable aid in gauging the severity and course of infections.

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**TRICHINIASIS. A DISCUSSION, WITH REFERENCE TO ELEVEN
RECOVERED CASES IN A FAMILY.**

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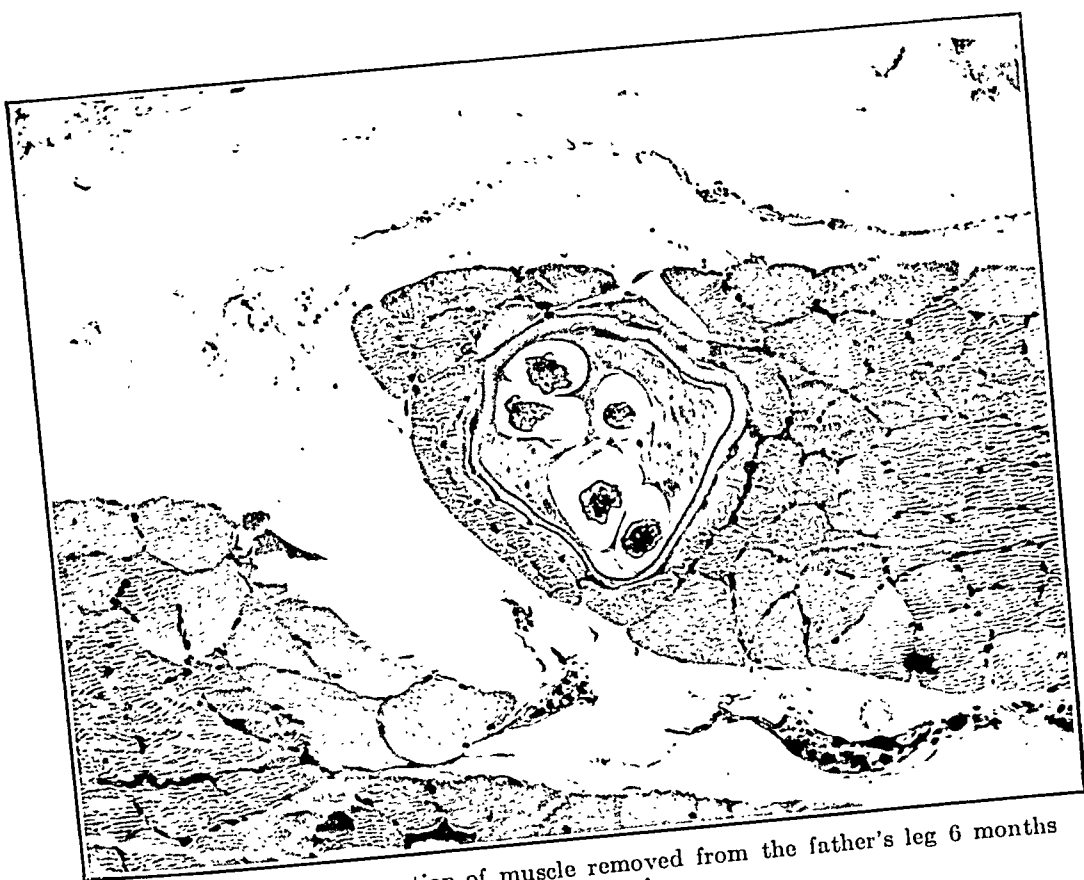
TRICHINA infection, not a rarity in recent years with the rigid governmental regulations of commercial meat products, is always of sufficient interest to claim the physician's attention. This is true because of the fact that the disease is preventable, it presents a variable and interesting clinical picture, it is now one of the reportable diseases, there is no specific treatment once the larvæ have invaded the voluntary muscles and, if a sufficiently large number of the parasites are ingested, the outcome may be fatal.

Historical. In the latter half of the 19th century there arose no little controversy as to the names of those investigators who should receive credit for the discovery of the parasite causing trichiniasis. The literature of that period abounds with bitter comments, particularly between the English and German writers, and shortly afterward the discussion was continued in this country. When one recalls that the public health aspect of trichiniasis was responsible for considerable international friction¹ it is not surprising that prejudices of personal opinion in this regard might have been entertained.

Any dispassionate survey of the literature can hardly afford to omit the name of Tiedemann² who, in 1821, observed small, calcified bodies in the muscular system of a man who had died of "thoracic dropsy." He described these bodies as being "from two to four lines long and round" and submitted the result of their chemical nature, the latter indicating that, in addition to their calcareous constituents, they contained organic matter resembling "albumen or fibrin."

This remarkable observer has been partially discredited only because of his statement as to the size of the calcified bodies, obviously much larger than is actually the case. It seems likely, however, that his was the first published record of the encysted trichina larvæ.

In 1828 Peacock³ noted the calcified specks in a case at autopsy,



Photomicrograph of a section of muscle removed from the father's leg 6 months after infestation.

prepared a specimen from the sternohyoid muscle and placed it in the museum of Guy's hospital. Five years later Hilton,⁴ another Englishman, discovered what was unquestionably the encysted larvæ and suggested their parasitic nature. In 1835 Prof. Richard Owen⁵ described a parasite of man, under the name of *trichina spiralis*, certain small worms which had been found by Paget, then a medical student, in a cadaver in London. Owen generously stated that Wormwald, a demonstrator in the anatomy laboratory, had previously pointed out to him that on numerous occasions sandlike particles in the muscle systems of postmortem specimens had dulled his dissecting knives. Joseph Leidy,^{5a} one of the greatest American biologists of the 19th century, was the first to find *trichina spiralis* in hogs (1846). Herbst (1851-1852),⁶ an experimental physiologist in Göttingen, appears to have been the first to have experimented with the life history of the parasite. In 1860 Professor Zenker⁷ of Dresden showed it to be the cause of a disease that has since been named trichinosis, and which prior to his observations had been confounded with typhoid fever and other maladies. The brilliant observations and experiments of Zenker,⁷ Leuckart,⁸ Virchow,⁹ and others thus placed the medical profession in possession of detailed data concerning the life history of, and source of infection by, the parasite under discussion; also the symptoms, duration and other clinical details of the disease and the preventive measures to be adopted.

In 1896 Brown¹⁰ pointed out the eosinophilia that has since been regarded so characteristic of the disease. Opie,¹¹ experimenting with guinea pigs fed with trichinous meat, noted the variations in the eosinophilic cells in mild and severe infections. Frothingham¹² described the intestinal lesions in rats, and later¹³ noted that in the human the larvæ enter by the lymph stream and are distributed by the circulating blood. In 1909 Herrick¹⁴ and Janeway recovered the larvæ from the circulating blood; 5 years later van Cott and Lintz¹⁵ first observed their presence in the cerebrospinal fluid. *in vivo*.

Recently we have been permitted to study 11 cases of trichinosis in a family. A summary of the history is as follows:

Case Reports. On April 30, 1930, an Italian father at Clyde, N. Y., purchased smoked ham from a local grocer. (The product was obtained from a well-known commercial meat packing company.) That evening the father, mother and their 9 children ate sandwiches made from the uncooked ham. Four days later the entire family became ill with nausea and diarrhea. (The remainder of the above-mentioned ham was sold to other patrons for frying purposes and no illness resulted therefrom.) These symptoms, together with lassitude, persisted for 6 days, when one of us (G. S. A.) was called to attend the mother. She presented nausea, marked prostration, a rapid pulse and a temperature of 103° F. The following day she was improved and the family physician was asked to discontinue his visits. On May 21, 1930, 18 days after the onset of the illness, the

father consulted his physician because of weakness and anorexia. Marked edema of the eyelids was noted and a differential blood count revealed 23 per cent eosinophils. That afternoon we examined the family, all members of which showed some evidence of the disease. The prominent symptoms of which all complained were: Nausea, diarrhea, pain in the legs, shoulders and back. The entire group had, or had had, edema of the eyelids and of the face over the malar regions. The following résumé is a summary of the interesting features of each case, including the observations made 6 months later.

FATHER, aged 45 years. Complaint: Severe pain in the shoulders, weakness and anorexia. Examination: Prostration, sweating, edema of eyelids, marked tenderness of shoulder and leg muscles. Temperature, 99.2° F. Eosinophils, 23 per cent. Progress: May 23: Palpable spleen. May 25: Developed hoarseness and cough; bronchopneumonia followed; Weakness persisted until latter part of June. November 21: Feels well; palpable spleen; slight tenderness of right leg; eosinophils, 4 per cent.

MOTHER, aged 33 years. Complaint: Weakness and exhaustion. Examination: Tenderness over suprascapular regions and in leg muscles. Temperature, 99.6° F. Eosinophils, 33 per cent. Progress: Diarrhea continued until July 1. Muscular pains and epigastric pains after eating were moderately severe during the first week in June. November 21: Slight tenderness of legs; palpable spleen; eosinophils, 7 per cent.

MARIE, aged 11 years. Complaint: None. Examination: Slight edema of eyelids; tender, tense, swollen leg muscles. Temperature, 103° F. Eosinophils, 10 per cent. Progress: May 24: Developed cough; no râles heard. May 28 to June 15: Upper abdominal pain after eating. November 21: No symptoms or signs. Eosinophils, 1 per cent.

IRENE, aged 10 years. Complaint: Pain in the legs. Examination: Slight edema of the eyelids; tenderness over suprascapular regions; legs are tense and slightly tender. Temperature, 100° F. Eosinophils, 13 per cent. Progress: May 27 to June 25: Occasional epigastric pain after eating. November 21: Feels well; palpable spleen; eosinophils, 8 per cent.

FRED, aged 5 years. Complaint: "Legs feel cold." Examination: Marked edema of eyelids; tenderness in legs, forearms and arms. Temperature, 100.6° F. Eosinophils, 14 per cent. Progress: May 23: Hoarseness. May 24: Palpable spleen. May 25: Upper abdominal pain, usually after eating. June 15: Indefinite abdominal pain after eating. November 21: Feels well; palpable spleen; eosinophils, 13 per cent.

JAMES, aged 9 years. Complaint: Pain in the shoulders. Examination: Slight edema of eyelids; tenderness over suprascapular regions. Temperature, 100.8° F. Eosinophils, 28 per cent. Progress: May 24: Epigastric pain after eating. May 25: Severe epigastric pain after eating. June 14: Abdominal cramps in the morning. November 21: Pain and tenderness in legs; palpable spleen; eosinophils, 5 per cent.

SAM, aged 13 years. Complaint: Weakness and lameness of legs. Examination: Pallor, edema of left eyelids; hoarse cough; palpable, non-tender spleen. Temperature, 102.2° F. Eosinophils, 28 per cent. Progress: May 27: Palpable spleen; irregular pulse. May 28: Dry cough. May 29: Edema of right side of face. May 31: Pallor. June 2 to 4: Abdominal pain after eating. June 15: Occasional abdominal cramps after eating. November 21: No complaints; palpable spleen; eosinophils, 3 per cent.

AGNES, aged 7 years. Complaint: None. Examination: Marked edema of eyelids; tenderness of left leg. Temperature, 99.2° F. Eosinophils, 21 per cent. Progress: May 21: Nightsweats. May 27 and 28: Epigastric pain after eating. June 4: Diffuse abdominal pain. June 15:

Occasional epigastric pain after eating. November 21: Feels well; edema of face and eyelids; palpable spleen; eosinophils, 9 per cent.

GEORGE, aged 15 years. Complaint: Weakness. Examination: Tenderness in legs. Temperature, 98.6° F. Would not permit drop of blood to be taken. Progress: Mild course. Would not allow further examinations.

MARGARET, aged 14 years. Complaint: Pain in left leg. Examination: Tenderness of left leg; edema of eyelids. Temperature, 99.2° F. Eosinophils, 38 per cent. Progress: May 24: Night sweats; palpable spleen. May 25 to 27: Feels well. May 28 to June 2: Epigastric pain soon after eating. November 21: No symptoms or signs; eosinophils, 2 per cent.

ANN, aged 2 years. Complaint: None. Examination: Slight edema of eyelids. Temperature, 98.6° F. Eosinophils, 38 per cent. Progress: Mild course; had sweats, pain in legs and edema of lids. November 21: No symptoms or signs; eosinophils, 5 per cent.

TABLE 1.—DIFFERENTIAL COUNT 18 DAYS AFTER INFESTATION.

Patient.	Age, yrs.	Polymorpho-nuclears, per cent.	Large and small lymphocytes, per cent.	Transitionals and large monocytes, per cent.	Eosinophils, per cent.	Basophils, per cent.
Father . . .	45	64.0	11.0	2	23.0	1.0
Mother . . .	33	42.0	18.0	7	33.0	0
Marie . . .	11	60.0	25.0	5	10.0	0
Irene . . .	10	51.0	31.0	5	13.0	0
Fred . . .	5	56.0	27.0	3	14.0	0
James . . .	9	50.0	20.0	2	28.0	0
Sam . . .	13	55.0	15.0	2	28.0	0
Agnes . . .	7	63.0	13.0	2	21.0	0
Margaret . .	14	38.0	21.0	1	38.0	2.0
Ann . . .	2	34.0	28.0	1	37.0	0
Average	51.3	20.9	3	24.5	0.3

TABLE 2.—DIFFERENTIAL COUNT 6 MONTHS LATER.

Patient.	Age, yrs.	Polymorpho-nuclears, per cent.	Large and small lymphocytes, per cent.	Transitionals and large monocytes, per cent.	Eosinophils, per cent.	Basophils, per cent.
Father . . .	45	58.0	35.0	3.0	4.0	0
Mother . . .	33	60.0	31.0	1.0	7.0	1.0
Marie . . .	11	55.0	41.0	3.0	1.0	0
Irene . . .	10	45.0	42.0	4.0	8.0	1.0
Fred . . .	5	35.0	47.0	4.0	13.0	1.0
James . . .	9	64.0	30.0	1.0	5.0	0
Sam . . .	13	45.0	47.0	3.0	3.0	2.0
Agnes . . .	7	43.0	46.0	2.0	9.0	0
Margaret . .	14	59.0	36.0	3.0	2.0	0
Ann . . .	2	40.0	53.0	2.0	5.0	0
Average	50.4	40.8	2.6	5.7	0.5

At various times during our observations we attempted to gain permission to excise a portion of muscle for microscopic diagnosis

but were unable to do so until 6 months after the onset of the illness. Illustration* is a photomicrograph showing the encysted trichinae in a section of muscle removed from the father's leg.

Table 1 is a summary of the differential blood counts made on May 21, 1930, 18 days after the family became ill. In Table 2 are recorded the differential counts made on November 21, 1930, 6 months later.

Discussion. Certain features of these cases seem of sufficient interest and importance to warrant further consideration.

1. *Eosinophilia.* Eosinophilia has been considered of diagnostic importance since Brown's¹⁰ first observations in 1896, and since whose contributions the presence of an eosinophilia has come to be regarded by many as essential in the diagnosis. However, although characteristically true, it is not an invariable finding, as a review of the literature clearly shows that many serious cases of trichina infection have occurred in which no eosinophilia was present. We have therefore regarded it of interest to review the more important observations that have been made on this subject.

T. R. Brown's¹⁰ original case showed 68.2 per cent eosinophils. Barker¹⁶ and Thayer,¹⁷ commenting on this case, declared this unusual blood picture to be unique in medical literature. One year later Thayer¹⁸ cautiously expressed the opinion that until further studies had been made, it could hardly be said that trichiniasis was the only type of myositis that might have an associated eosinophilia. In 1898 Brown¹⁹ published his important monograph and concluded that "there is a marked increase in the percentage of eosinophilic cells in the blood . . . this increase may be used as a diagnostic sign in the disease." Thompson²⁰ later believed that "a high degree of eosinophilia is invariably present; usually 30 per cent and frequently much higher, even above 80 per cent." Leen²¹ thought that the eosinophilia stood in close relation to the migration of the embryos and their entrance into the musculature, and that for months or even years after recovery these cells were increased. Cabot²² mentioned a case in which there was no increase in the eosinophils until 10 days after the onset of the disease. It will be recalled that all of our cases showed a distinct eosinophilia during the third week. (Table 1.)

Opie,¹¹ working with guinea pigs fed with trichinous meat, was led to believe that there was no constant alteration of the number of eosinophils until the end of the second week after infection, when the relative and absolute number rapidly increased and reached a maximum at the end of the third week. He was of the opinion that the number of eosinophilic leukocytes in the blood always diminishes before death, so that the proportion was usually less than 1 per cent. He further concluded that infections with a very large number of parasites caused a rapid diminution of the eosin-

* Specimen prepared by Department of Pathology, Syracuse University College of Medicine.

ophils and was quickly fatal, whereas mild infections stimulated these cells to active multiplication.

Gregg²³ reported the case of a boy who had only 10 per cent eosinophils after 3 weeks of the disease and believed at that time there was no parallel case in the literature. DaCosta²⁴ later cited a patient without fever or history of infection in which trichinae were found in an inflamed leg muscle and in which no eosinophilia was present. Bartlett's²⁵ case showed only 1 per cent eosinophils before death. Howard²⁶ reported a fatal case without eosinophilia but with a large number of eosinophils in the muscle lesions. McDonald and Waddell²⁷ reported 43 cases in which 12 per cent did not show an eosinophilia. Other observers^{15, 20, 28} were of the opinion that the degree of eosinophilia afforded no accurate index of the severity of the disease. The observations in our non-fatal cases would tend to support this latter opinion. Weiss²⁸ commented that "the prognosis is poor when there is a sudden drop in the eosinophil count." Jaisohn²⁹ concluded from a study of an epidemic that the sudden subsidence of leukocytes and reduction of eosinophils indicated an unfavorable termination. Recently Aldridge³⁰ has reported a series of 29 cases, all of whom had a definite eosinophilia except the 2 patients who died.

It therefore becomes apparent that an eosinophilia is not a constant or invariably dependable finding in trichina infections. As has already been pointed out, it may be absent during the entire course of the disease; again, the increase in the relative numbers may not be present until 1 to 3 weeks after infection. It has never been established that the degree of eosinophilia bears any relationship to the severity of the disease except, possibly, in the fatal cases. A review of the literature suggests that those cases failing to exhibit an eosinophilia at all times during the acute stages of the disease are to be regarded as the ones most unlikely to recover. The suggestion is offered that a more general appreciation of the above observations might prevent serious errors in diagnosis and prognosis.

2. *Palpable Spleen.* One of the most interesting features noted in our cases was the splenic enlargement. Some years ago, when trichiniasis was more frequently confounded with typhoid, the absence of a palpable spleen was thought to be a point of differentiation in favor of the former. Neither Osler³¹ nor Cecil³² mentions the presence or absence of a palpable spleen in a discussion of trichiniasis. It is of some interest that 1 of the 3 cases Brown¹⁹ described in 1898 had a palpable spleen, although no further comment was made concerning its presence.

Frothingham¹³ described a case that came to autopsy in which there was no splenomegaly. Leen²¹ declared the spleen not to be enlarged in trichiniasis, but that if it were found to be palpable, it was due to a mixed infection and not a peculiarity of the disease. van Cott¹⁵ noted no enlargement in 10 cases.

At the time of our first examination, during the third week of the illness, in only 1 case was a palpable spleen discovered, (Sam, aged 13). Two days later one of us (G. S. A.) found a palpable spleen in the father. The following day the spleen was palpable in 2 more of the cases (Fred, aged 5 and Margaret, aged 14). All of the cases were observed daily until June 15 without further evidence of splenic enlargement in the remaining cases.

Because of their apparent recovery they were not seen again until 5 months later (November 21, 1930), at which time we examined the 10 available cases and found that 7 of them had a palpable spleen. Except in 1 case (Margaret, aged 14), all of the cases who developed a palpable spleen during the active stage of the disease also presented this finding 6 months later. Eight of the cases, then, had a palpable spleen at one time or another during the period of our observations, and 4 cases had a palpable spleen during the third week, at a time when the symptoms of their illness were most acute. We were unable to make a final examination of 1 patient (George, aged 15) because of his incorrigible attitude.

The presence of a palpable spleen is of considerable interest, and its significance is indeed difficult to evaluate. It is hoped that these observations may be borne in mind by others who may see cases of trichiniasis. Possibly careful studies on those cases coming to necropsy may offer a definite explanation of the phenomenon.

3. *Diagnosis and Symptomatology.* The usual picture of trichiniasis offers little difficulty in diagnosis. Most frequently cases are seen in groups and a common source of infection is ascertained. The characteristic symptoms of gastrointestinal irritation, the fever, the muscular pains, the edema of the eyelids and the eosinophilia are noted in the majority of nonfatal cases when sufficient trichinous meat has been eaten.

It is certainly true that isolated, unrecognized and atypical cases of trichiniasis do occur and occasionally there is no history of infection in proven cases of the disease. We recall the instance of one family in which the mother became infected although the father and four children escaped. All had eaten of the same piece of insufficiently cooked, home-cured pork. As early as 1901 Williams³³ reported finding trichinae in 5.3 per cent of 505 unselected autopsies. All of the subjects had died of other disease than trichiniasis, hence "the infection with trichinae must, in every case, have occurred a considerable time previously." Conner³⁴ has recently drawn attention to the atypical forms of trichiniasis. "Trichiniasis presents a clinical picture of much greater variability than is the case of most specific diseases," he says, and concludes that there are cases that run an afebrile course and that in some patients the characteristic eosinophilia may be lacking; that some cases may resemble acute nephritis, acute meningitis or sinusitis; that other patients may exhibit conspicuous and alarming throat symptoms and others may have epigastric pain as the chief or only symptom of the disease.

MacKenty³⁵ has focused attention on the cases with predominating laryngeal symptoms. Such patients, he says, may have cough, pain on swallowing and on phonation, and a harsh voice. A point of some interest is that the edema of the throat and larynx in his cases appeared more like passive edema rather than that due to an acute surface inflammation. Thomas³⁶ and Pratt³⁷ have described rather atypical cases of trichiniasis in which the predominant symptoms are referable to the sinuses.

The gastrointestinal and abdominal symptoms are subject to considerable variation and are of great interest to the physician who attempts to evaluate their probable causes. It is likely that the early symptoms of nausea, diarrhea and vomiting are due to mechanical irritation of the intestine at a time when the parasites are penetrating the mucous membrane. Frothingham¹² has demonstrated the manner of this invasion and pointed out that some of the epithelium, where stripped off, becomes necrotic. In spite of this fact, diarrhea is by no means a constant symptom. Thompson²⁰ suggested that it occasionally occurs as an immediate symptom when it appeared due to botulismus rather than to irritation by the trichinæ. All of the cases reported in our series had diarrhea during the first week of the disease, but only 1 case, the mother, had the symptom after the second week. In her case the diarrhea persisted for more than 2 months.

The variety of the types of abdominal pain in any group of cases is fascinating. Possibly the early cramplike abdominal pains, during the period of invasion, are due to localized intestinal spasm. When one reflects that the larvæ have been found in the mesenteric lymph nodes³⁸ and for a time are abundant in the peritoneal cavity;³⁹ that the embryos may break out of the vessels in the liver and pancreas¹⁸ and cause local destruction of tissue; and finally that death usually occurs as the result of penetration of the intestinal wall,³⁹ it is not difficult to agree that no typical abdominal distress could be anticipated in any case or group of cases. It was of interest that the majority of our cases complained of abdominal pain, chiefly epigastric and usually after eating, about 3 weeks after their infection. No spasm or rigidity of the abdominal muscles was noted. One patient (James, aged 9) had the mild epigastric pain at the same time as the other cases, but 2 weeks later began to have severe abdominal colic each morning between 8 and 9 o'clock. The pain was severe, the temperature normal, the distress had no relation to the ingestion of food. The paroxysms lasted from $\frac{1}{2}$ hour to 1 hour, the boy cried and rolled about on the bed and always vomited whatever was given by mouth to ease the discomfort. No localized tenderness or spasm could be elicited and after the paroxysm he remained free from pain for the remainder of the day.

It has long been recognized that many cases of trichiniasis may have respiratory symptoms. To Opie¹¹ and Frothingham¹³ we owe our conception of the pathologic processes taking place in the lungs.

One of our cases had a definite bronchopneumonia. Five cases developed a cough without rise in temperature and 3 cases presented rather marked hoarseness. The laryngeal pathology in these cases has been referred to elsewhere.³⁵ MacCallum³⁹ has called attention to the bronchitis in some of the fatal cases.

4. *Laboratory Aids in Diagnosis.* The variations in the presence, degree, or absence of eosinophilia has already been discussed. Following Staübli's^{40,41} work, Herrick and Janeway⁴⁴ demonstrated the presence of trichina embryos in the circulating blood. Their method was to take the blood with 10 to 15 parts of 3 per cent acetic acid, centrifuge and examine the sediment microscopically. Obviously this method is of value only during the period of migration.

Formerly the presence of a positive Widal test was thought to differentiate definitely between typhoid and trichiniasis. This cannot be said to be invariably true, since Maase and Zondek⁴² have reported 3 cases of trichiniasis with positive Widal's, and Conner³⁴ has drawn attention to the fact that rarely the differentiation from typhoid may be rendered difficult by the presence of a strongly positive Widal reaction. It is of interest that 1 of Brown's¹⁹ 3 cases had a positive Widal, but it was said this patient had had typhoid fever 6 months previously.

Since Van Cott and Lintz¹⁵ first reported the finding of embryo trichinae in the spinal fluid *in vivo*, many other workers^{27,43,44,45,46,47,48} have confirmed the observations. Apparently trichiniasis may present the clinical picture of acute meningitis and Meyer⁴⁴ has pointed out that in cases in which the embryos have been found in the spinal fluid the cell counts varied between 40 to 240 lymphocytes per c.mm. His warning in this regard was that in such instances it might be difficult to differentiate between poliomyelitis, were it not for the presence of the embryos in the cerebrospinal fluid.

There is considerable variation of opinion as to the presence of the parasites or embryos in the stools of patients suffering with trichiniasis. Most observers^{15,20,27} agree that the parasites or ova are not to be found in the stools. As early as 1864 Fiedler⁴⁹ made the suggestion that the adult parasites were dissolved in the small intestine and therefore were not to be discovered in the stools. Van Cott and Lintz¹⁵ have expressed a similar view. Other writers^{15,50,51} were of the opinion that the embryos were not to be found in the stools since they were not discharged into the lumen of the intestine. Stitt⁵² states: "During the diarrheal stage we may examine the stools for adult worms, in particular dead males or possibly actively motile embryos." Osler³¹ declares: "The worms may be found in the stools or in the duodenal contents." Weiss⁵³ has recently reported the finding of both the adult parasites and ova in the stools. Only 1 of our cases had a diarrhea at the time we saw the patients but we were unable to demonstrate the presence of adult parasites or their embryos in her stool specimens. The review of the literature suggests that the detection of the parasites or the

embryos is of infrequent occurrence and that therefore the examination of the stools offers little diagnostic data as compared to other, more regularly dependable laboratory procedures.

Summary. 1. Eleven recovered cases of trichiniasis in a family are reported.

2. Marked eosinophilia was present in each case.

3. A review of the literature, with reference to the diagnostic importance of eosinophilia, is presented. Attention is directed to the fact that eosinophilia is not a constant and infallible diagnostic criterion.

4. A palpable spleen was noted in 4 of the 11 cases during the first 3 weeks of the disease; 6 months later 7 of 10 cases had a palpable spleen.

5. A brief discussion of the symptomatology, clinical manifestations and the diagnostic criteria of trichinosis is presented.

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PRIMARY ANGIOFIBROMA OF THE DIAPHRAGM.

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As Lucké¹ has shown, primary tumors of the diaphragm are rare, less than a score having been reported. All of these have been of connective tissue origin, namely, fibromas, chondromas, lipomas and sarcomas. The purpose of this paper is to report an additional case, that of an angiofibroma.

Case Report.—J. S., a white male, aged 50 years, was admitted to the Tuberculosis Service of the Philadelphia General Hospital, November 12, 1931. His history and clinical course were typically those of extensive pulmonary tuberculosis. Physical examination showed extensive involvement of both lungs and the sputum was positive for tubercle bacilli. No other findings of significance were noted.

Roentgenologic reports were as follows: Both lobes of the left lung show considerable irregular density; two radiolucent areas are present in the left upper lobe; the left diaphragm is not visualized; the upper portion of the right upper lobe, especially in the infraclavicular region, shows marked irregular density, the remainder of the lobe being mottled to a lesser degree; the right apex also shows a radiolucent shadow; the heart is displaced to the left; in the anteroposterior view the mesial half of the right diaphragm is the seat of a large, well-defined shadow, the upper border of which is convex; the base measures 8 cm. (Fig. 1). On profile view, this shadow is somewhat rectilinear in shape, measuring approximately 11 by 4 cm.; it extends from the xiphoid dorsalward to a point just posterior to the mid-axillary line (Fig. 2). Fluoroscopic examination shows this tumor mass to move synchronously with the diaphragm. Roentgen diagnosis: Extensive ulcerative fibrocaceous tuberculosis of left lung and upper lobe of right lung, with cavitation of both upper lobes; atelectasis of left lower lobe; neoplasm arising either from right diaphragmatic pleura or right dome of liver.

Much discussion arose regarding the situation of the tumor. The majority ruled that its origin was below the diaphragm, although one of us felt that it lay above. Tumor of the diaphragm *per se* was not considered.

The patient grew progressively weaker and died December 5, 1931.

Necropsy examination (No. 23,669) confirmed the clinical diagnosis of pulmonary tuberculosis. Aside from the tumor to be described below the gross examination showed no features of interest.

The shadow described in the roentgenogram was cast by a tumor lying *between* the leaflets of the right dome of the diaphragm. It measured 12 by 6 by 5 cm., was irregularly rounded and extremely firm. The cut surface showed a tough, grayish-white matrix, mottled by many roughly round hemorrhagic areas most marked near the center (Fig. 3). There was a depression in the posterosuperior surface of the right lobe of the liver,

thus forming a nest into which the inferior surface of the tumor fitted snugly.

Sections were removed from a number of portions of the tumor and the tissues stained by azo-carmin, Heidenhain's hematoxylin and by Mallory's connective tissue stain, in addition to the usual preparations. A definite capsule was present. The bulk of the tumor mass was composed of loose (Fig. 4-A) to dense interlacing bundles of fibrocytes that showed little growth activity (Fig. 4-C). Many areas had become acellular, varying in density from a delicate, lacy, fibrillar structure to dense, coarse collagen bundles. Some portions of the tissue were necrotic. The areas that had appeared hemorrhagic on gross inspection were seen in section to be masses of well to poorly defined blood channels, closely packed and not well marginated by the fibrous tissue in which they lay. Many of the angiomatous masses were cavernous (Fig. 4-B). The fibrous portions were quite vascular *per se* and contained some free hemorrhage. No muscle, cartilage or other tissue elements were present to suggest a teratoid nature of the tumor.

SUMMARY. A case of primary angiofibroma of the diaphragm is described.

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FACIAL DIPLEGIA IN POLYNEURONITIS.*

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FACIAL diplegia may occur in any form of multiple neuritis, although it is most frequently seen in that form of the disease produced by infections, of which there is one with a special tendency to involve the seventh and other cranial nerves. Holmes¹ and Bradford² observed cases of this form of polyneuritis during the World War; Yudelson³ of Chicago and Viets⁴ of Boston wrote illuminating articles upon this condition, their papers appearing in 1927. Although polyneuritis is a fairly common condition, involvement of the cranial nerves is rather unusual, however if investigated more often, it would probably be found that the optic nerves are frequently affected. In many of the cases of the infectious

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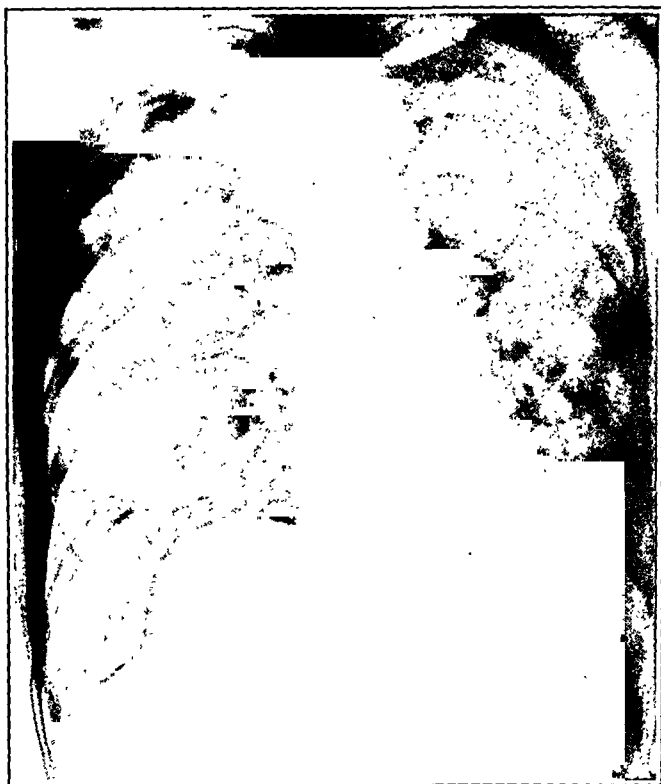


FIG. 1.—Roentgenogram (anteroposterior view). Note tumor mass projecting into right lower lung field.

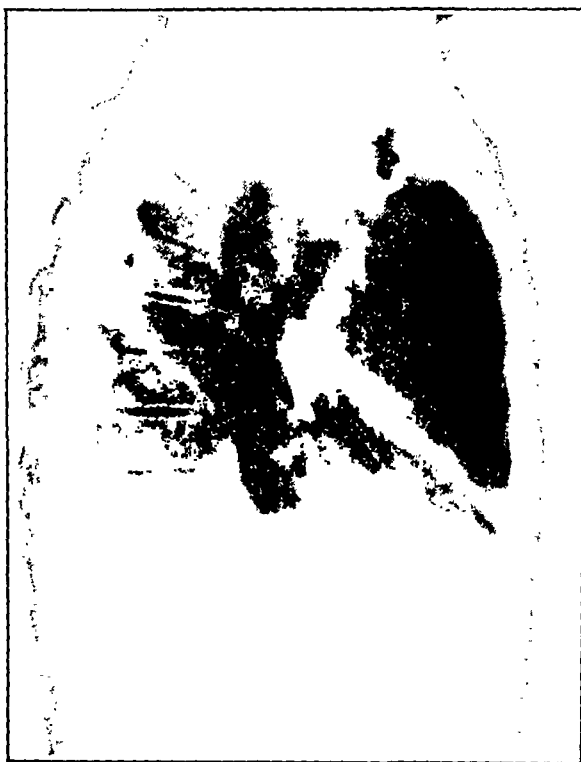


FIG. 2.—Roentgenogram (right lateral view).



FIG. 3.—Tumor mass (cut open, showing hemorrhagic central zone).

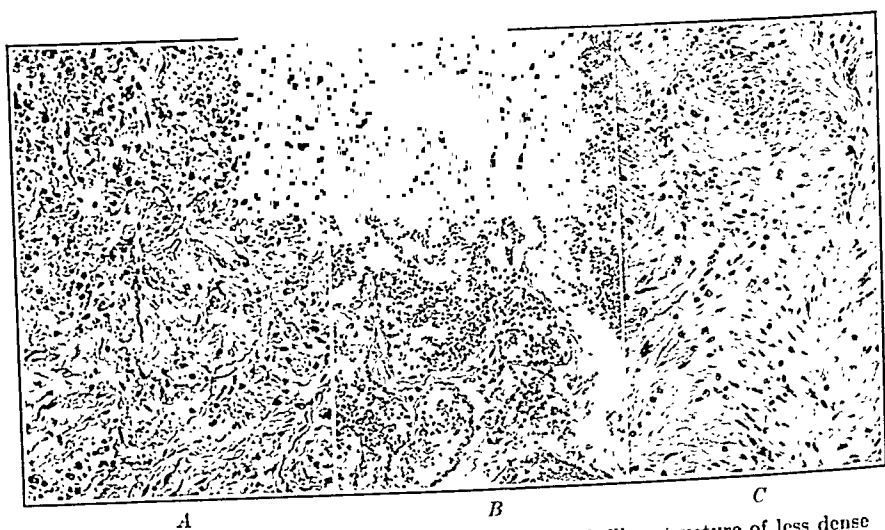


FIG. 4.—Histologic structure of tumor: A, lacy, fibrillar structure of less dense portion (150 X); B, angiomatous area showing large cavernous blood sinuses (150 X); C, predominating structure of dense interlacing bundles of fibrous tissue (150 X).

type of multiple neuritis with cranial nerve palsies, there is a distinct ascending element to the paralysis which, beginning in the feet, involves rather rapidly the rest of the lower extremities, then the upper and finally the face. This picture suggests strongly the syndrome called Landry's paralysis. In most of the cases there is a history of a slight illness from 4 days to 6 weeks before the onset of the nervous symptoms. Pain in the back, headache, vomiting and fever from 100° to 101° F. were common symptoms during the febrile stage. Then days or weeks later, in this way resembling very much the palsies that come on after diphtheria, the patient develops tingling and numbness followed by paralysis in 2 or 3 days. In many of the cases the weakness is greater in the proximal segments of the limbs, thus differing greatly from the distribution of the early paralysis seen in the ordinary case of multiple neuritis. In some cases described the patient was totally paralyzed at the shoulders and hips but could move the fingers and toes freely. Facial diplegia was almost constantly seen in Bradford's cases, and he thinks because of the symmetrical weakness it may have been overlooked in others. The sphincters were involved in Holmes' cases, whereas in Bradford's series this did not happen. Complete recovery was often slow, taking as long as 6 months. In Bradford's 30 cases death occurred in 8, from 5 to 12 days after the onset of the paralysis. The cause of death was attributed to weakness of the pulmonary muscles and the diaphragm, although no case of massive collapse of the lungs was found. One of our cases had distinct respiratory embarrassment a few days after the onset.

The microscopic examinations made by Holmes, Bashford⁵ and Viets were directed largely to the central nervous system where minute and widely diffuse hemorrhages were present, especially in the spinal cord. Viets found the cells of the seventh nuclei normal in number but almost all with marked structural changes. They were swollen and distorted and many had lost their polygonal form; in addition chromatolysis was extensive with occasional displacement of the nucleus. Cells of the adjacent cranial nerves were ordinary, and sections through the pons and medulla showed no variation from the normal. Throughout the spinal cord in Viets' case the vessels were markedly congested; no mention is made of the study of the peripheral nerves themselves. In Bashford's report the only gross finding of importance was meningeal congestion with some edema of the brain and cord, which Bashford thinks may have been terminal or perhaps associated with respiratory embarrassment. Cross sections showed minute hemorrhages. On microscopic examination the peripheral nerves showed an irregular involvement, most marked in the sciatics. The spinal cord revealed minute and widely diffused hemorrhages in the dorsal enlargement, extensive and advanced interstitial cellularity in both cervical and lumbar

enlargements. The central neural canal showed considerable proliferation of the ependymal cells. The nerve cells of the various tracts, including both the anterior and posterior horns, were irregularly involved. Some of the specimens showed involvement of the posterior roots. Of the portions of the brain examined, all had a slight degree of round cell infiltration, most pronounced around the large antler cells of the cortex, and on the whole greater in the deeper than in the superficial gray matter. There was also pneumonia, and congestion of the liver, spleen and kidneys.

Bashford successfully transmitted the disease from man to monkey and from monkey to monkey by subdural inoculation of an emulsion of the human cord of a fatal case and from the fresh cord of the first monkey to another and later by a pure culture. Wilson⁶ isolated the organism and found it to be a minute, rounded or kidney-shaped body, measuring 0.2 to 0.5 μ in diameter; he considers that it shows a marked resemblance to the globoid bodies described in anterior poliomyelitis. From the pathologic reports it will be seen that while extensive studies were made of the central nervous system, comparatively little attention was paid to the peripheral nerves, although the disease is reported as acute polyneuritis. The reports also make it very evident that while the brunt of the affection may be borne by the peripheral nervous system, the central parts do not escape, in fact, they may be more involved than the peripheral.

Patrick,⁷ in 1916, reported 3 cases of facial diplegia occurring in the course of multiple neuritis, in one of which there was a history of an acute febrile disorder previous to the onset of the neuritis.

While it is true that most of the cases of polyneuritis complicated by facial diplegia are due to infections, they are not all due to the special infection mentioned above; facial diplegia may occur in any case of multiple neuritis no matter what the cause. For example, one of our cases about to be reported was apparently due to a combination of gonorrhea and pronounced dental infection. Occasionally facial diplegia may occur in the course of multiple neuritis due to alcohol. Before prohibition in this country, we saw on the service of Dr. W. G. Spiller at the Philadelphia General Hospital, a case of multiple neuritis in which facial diplegia occurred. The man had been drinking to excess of an extremely poor grade of whisky.

Report of Cases. CASE 1.—A white, single girl, aged 17 years, with a negative past and family history, was taken ill on December 8, 1928, with an acute cold involving the upper respiratory tract and accompanied by fever and pain in the back of the neck. She was seen by Dr. H. J. Cloud, of Ardmore. Evidence did not exist of pulmonary involvement, and while the patient was uncomfortable she was not seriously ill. Three or 4 days after the onset she complained of numbness in the fingers and toes, and these paresthesias gradually ascended the extremities. With the appearance of the paresthesias in the extremities she noticed what she called

a "stiffness" involving the central part of the face. Diplopia was not present and the eyesight and hearing were normal. She had no headache but vomited twice 2 days after the onset and was delirious on one occasion. The pupils were irregular, the left slightly larger; both reacted sluggishly. The ocular movements and those of the face, palate, tongue and jaws were normal. The neck was slightly stiff and Kernig's sign was present bilaterally. The deep reflexes were lost with the exception of the patellars, which were diminished. Plantar stimulation produced no response, whereas the abdominal reflexes were normal. A blunting of sensation for all forms was present in the distal portions of the extremities. The temperature had ranged from normal to 101° F.

Clinical Course. Two days later she was reexamined and a double facial palsy and complete paralysis of the palate were noted. The paresthesias were more pronounced in the extremities and distinct but slight weakness was noted in the distal portions. All the deep reflexes were absent and the sensory loss was more profound and covered a wider area in the extremities, although sensation in the face was normal. She was transferred to the University Hospital on December 16, 1928, and Dr. Alfred Stengel saw her in consultation. The nose and throat examination at this time revealed that the left vocal cord was almost motionless while the right had only fair motility. A considerable amount of pus was present in the nose and the palate was congested, glazed and covered with thick, tenacious mucopus. By January 4, 1929, laryngeal motility had returned to normal and the pharynx showed evidence of returning function. A Roentgen ray of the sinuses revealed clouding of the frontal and ethmoids on both sides; some thickening of the maxillary mucous membrane existed, especially the left; the sphenoid cells were negative. The Wassermann reaction, examination of the urine and a blood culture were negative. A culture from the nose and throat showed a heavy growth of staphylococci and streptococci but no Klebs-Loeffler bacilli. The temperature was elevated during the first 3 weeks of her stay in the hospital, but was usually below 101° F. Quite severe pain developed in the feet, which also became weak, more particularly in the extensors, and very tender to pressure. The hands also were weak and showed moderate wasting in the interosseous spaces. During the first 24 hours after her admission to the hospital distinct respiratory impairment occurred, but subsided. Moderate depression and intense insomnia were prominent symptoms for the first 3 weeks. She was discharged from the hospital on January 18, 1929, 44 days after the onset, in a greatly improved condition. Subsequently she made a complete recovery with the exception of slight persisting weakness with contracture of the lower part of the right side of the face. The deep reflexes returned much more quickly than after the ordinary case of multiple neuritis and became exaggerated, although positive signs of pyramidal tract involvement were never discovered.

A lumbar puncture was not done.

Comment. This patient had what seemed to be an acute cold complicated by ethmoid and frontal sinus disease. In addition to the ordinary signs of polyneuritis she had a double facial palsy, a complete paralysis of the palate, paralysis of the left vocal cord and weakness of the right. In addition she showed rather marked depression and insomnia. During convalescence the deep reflexes returned rather quickly and became exaggerated, although Babinski's sign was never found. The quick return of the reflexes and later their exaggeration, we believe, points to the involvement of the pyramidal tracts either in the cord or higher up. It is most likely that the cranial nerve palsies in this case were central in origin rather than peripheral.

CASE 2.—A white, married woman, aged 41 years, was admitted to the neurologic service of the Episcopal Hospital on May 23, 1924. She had had 6 children, 5 of whom were living and well; she had had one stillbirth. Her last child was born 10 weeks before the onset of her present trouble; the birth was normal. The question of her use of alcohol was thoroughly investigated and it can be asserted positively that she did not use the drug at all. She did not have an acute febrile disorder after the birth of her child. Her chief complaints were numbness, tingling and weakness in the hands and feet and inability to move the face. Her trouble dated back 4 weeks when paresthesias appeared in the fingers and toes and, while gradually spreading upward in the lower extremities, did not go higher than the fingers in the upper extremities. A week after the onset she had difficulty in walking because of weakness. Her condition slowly became worse and one week before admission, or three weeks after the onset, she became confined to bed, and shortly thereafter her face became "stiff" and paralyzed. For the first week she also had diplopia, the objects being placed side by side. She had no sphincter disturbance.

Examination. The pupils were equal, regular and reacted well to light and in accommodation. Except for a weakness of the right internal rectus muscle all the ocular nerves functioned well. Double vision was present when the patient looked to the left. A complete bilateral facial palsy was present with the loss of contraction of the muscles to faradism. The breath was heavy and offensive. The tonsils were small and buried and pronounced redness of the anterior pillars was noted. The lungs, heart and abdomen were normal. All of the deep reflexes were absent, the plantar reflexes were normal, but the abdominals could not be obtained. Lasègue's sign was present on both sides. Slight contracture in flexion was present at the knee joints. Bilateral foot drop was noted and a generalized moderate weakness was present in the muscles of the lower extremities and in the uppers below the elbows. Pressure along the course of the nerves and laterally to the feet produced marked pain. She had no trouble in chewing or swallowing. Mentally she was irritable but showed no evidence of a psychosis. A Roentgen ray of the teeth showed what was described as a "huge bone abscess" involving the upper left central and lateral incisors and canine and a root abscess about the upper right canine. A number of examinations of the urine showed hyalin and granular casts and on two occasions the urine showed many leukocytes. Blood chemical studies, routine examination of the blood and spinal fluid (with the exception of the colloidal gold curve which was 4432110000) and a culture of the throat for Klebs-Loeffler bacilli were all negative. A gynecologic examination revealed a chronic gonorrheal endocervicitis and urethritis. The vaginal and cervical smears showed many Gram-negative diplococci, both intra- and extracellular.

This patient gradually improved so that by August 4, 1924, she was discharged in good condition. The power had completely returned in her extremities and in her face, although she could not close the eyes tightly.

Comment. This patient was reexamined in October, 1930, and was entirely well except for weakness in closing the right eye, and the loss of the deep reflexes. She was never as acutely ill as our first case. We believe the etiologic factors here were gonorrhea and dental infection. It is likely that most of the symptoms in this case were due to peripheral nerve lesions, although the colloidal gold curve pointed to central involvement.

CASE 3.—A colored female, aged 23 years, was admitted to the neurologic service of the Philadelphia General Hospital, January 3, 1928, with the chief complaint of inability to walk. She was perfectly well until the latter part of August, 1927, when she began to suffer with severe, continuous headaches accompanied by chills and fever. In the middle of September

she noticed that she was extremely nervous and had pains in her joints. About the middle of December her face "swelled," became numb, and felt as if paralyzed. Then her legs became stiff and weak. Finding that she frequently fell, she remained in bed. Paresthesias developed in the hands, which at this time became paralyzed. Pain has been most severe in the hands, feet, knees and the elbow joints.

Her past medical history suggests that she was suspected at least to be syphilitic, because she was given 8 injections of neoarsphenamin at a hospital in January and February of 1927. Since that time she has had 2 negative blood Wassermanns. In addition there have been recurring attacks of tonsillitis for a period of 2 years, and diphtheria was contracted 4 years ago. One child born in March, 1927, is living and well. The patient has never had a miscarriage.

Examination. A facial diplegia with inability to pucker the lips, laugh, close the eyes tightly or wrinkle the forehead was found. The pupils were slightly irregular, the right being larger than the left; the eyes otherwise were normal. The tonsils were large, cryptic and diseased. The extremities showed bilateral foot- and wrist drop with inability to perform any motion whatsoever below the shoulders and hips. All of the deep reflexes were lost. No disturbance of sensation existed except extreme tenderness upon compression of fingers and toes and of muscles of arms and legs.

The laboratory examinations revealed a negative Wassermann in the blood and spinal fluid. The colloidal gold curve was 0122233333; there were 21 cells per c.mm. of spinal fluid, and a trace of globulin. Blood chemical studies, blood count, throat smears and culture for Klebs-Loeffler bacillus, and urinalysis were all negative. A cervical smear was negative for the gonococcus. The optic disks showed pallor of the temporal sides. Reactions of degeneration were present and widespread in both the upper and lower extremities and in the face.

Clinical Course and Outcome. This patient remained in the hospital for 10 months. At the end of the second month her tonsils were removed; they were found to contain several pockets of pus. Following their removal the temperature, which had been slightly elevated, became normal and remained so. Power began to return in the face about 6 months after admission to the hospital. When she left she had slight movement in her fingers and toes but could not stand, walk, nor feed herself. Two years after the onset power had improved in her lower extremities sufficient to enable her to stand and walk. She was reexamined on March 11, 1931. The face had entirely recovered. All movements were possible in the upper extremities, but there was some limitation of the motion at the metacarpophalangeal joints due to ankylosis. All movements in the lower extremities were possible, but extension of the toes and feet was not normal and the gait was of the steppage type. The muscles had not regained their full contour, but had improved greatly over the condition they were in when the patient left the hospital.

Comment. We believe the cause of this woman's nervous disorder was an infection which probably was present in the tonsils; following their removal the temperature dropped to normal and remained there. No evidence of infection could be found in the blood or endocardium, and while there may have been a blood stream infection at the onset, laboratory evidence of this could not be found. Careful cultures of the throat and tonsils were made in this as well as the others for Klebs-Loeffler bacillus.

On one occasion in the nervous wards of the Philadelphia General Hospital we saw 2 cases of multiple neuritis who had done poorly for weeks. Cultures of the throat revealed Klebs-Loeffler bacillus

in both cases, and after injections of diphtheria antitoxin and the removal of the tonsils both cases recovered.

Discussion. It is quite clear from the examination of cases of so-called polyneuritis complicated by cranial nerve palsies or not, and from a review of the literature on the subject, that there are many cases in which the central nervous system is involved as well as the peripheral. As far back as 1898, Mills⁸ proposed the term neuronitis for cases of this sort, although he said that it had an unnatural sound, even to a neurologic ear. Kennedy⁹ and Brock and Ivimey¹⁰ have described cases under this title. In the discussion of the paper, "On the Causation and Symptomatology of Multiple Neuritis," by T. Grainger Stewart,¹¹ S. A. K. Wilson said that the term "multiple neuritis" was a misnomer in many instances. He proposed that if no sensory symptoms were present the term neuronitis should be used, but if the lesions were multiple polyneuronitis would be appropriate.

Under the title of "Acute Ascending Paralysis Among Troops," Casamajor¹² described 2 cases comparable in many ways to those described by Bashford and others, and for which Casamajor hesitatingly proposed the term "Acute Infective Meningo-myeloneuritis."

As "Myeloradiculitis," Strauss and Rabiner¹³ wrote about a group of cases that might readily fit in with those that have been taken up in this paper. Most of their cases had had infections involving the upper respiratory tract before the onset of the symptoms indicative of the involvement of the roots and cord. The most extraordinary thing about these cases was the rapid improvement. Two French authors, Guillain and Barré, described in 1916 a syndrome with symptoms indicative of lesions of the spinal roots and peripheral nerves, and in some instances with signs suggesting spinal cord involvement. In fatal cases they found inflammatory lesions of the nerve roots, spinal ganglia, spinal cord and peripheral nerves.

Conclusions. Patients suffering from multiple neuritis occasionally have cranial nerve involvement, and the cranial nerve most frequently involved is the seventh. This may occur in ordinary multiple neuritis, which, as is well known, may be due to almost any toxic or infectious condition. However, there is a special neurotropic infection which may be closely allied to that of epidemic encephalitis or poliomyelitis, and which may involve not only the peripheral, but also the central nervous systems. In this condition cranial nerve palsies are especially likely to be found, and when present are probably more often due to involvement of the central than of the peripheral nervous system. The 3 cases which form the basis of this paper all occurred in women and all were due to infections. Cases 1 and 3, especially 1, conform rather well to the infectious type of polyneuronitis. While Case 2 was also infectious, it seemed to be due to a combination of gonorrhea and dental infection.

Confusion exists in the nomenclature because of the various headings under which this disease has been described. Due to the fact that the organism has a tendency to localize in different parts of the nervous system, individual investigators have given various names to the disease, depending upon what particular part was involved pathologically in their cases. Of all of the terms suggested to date, the most descriptive is that of Mills, "neuronitis."

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CEREBELLAR APOPLEXY.*

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HEMORRHAGE and thrombosis are infrequently limited to the cerebellum. Postmortem observations indicate an impressively low incidence of cerebellar apoplexy. The purpose of this presentation is to report 10 cases of hemorrhage in the cerebellum only, and to describe the clinical syndromes with their pathogenetic relationships. Two cases coming to autopsy at the Minneapolis General Hospital during 1930 stimulated a search of the hospital files, which yielded records of but 3 previous cases verified postmortem. A review of the reports on all cases of cerebral hemorrhage on file in the Department of Pathology, University of Minnesota, lead to the finding of 5 more cases. Frequency as indicated by postmortem records is shown in Table 1.

TABLE 1.—FREQUENCY OF CEREBELLAR APOPLEXY.

	Number of cases.	Per cent.
Autopsy records in the Dept. of Path. from 1897 to 1931	17,257	
Cases of cerebral hemorrhage	1,112	6.5
Cases of cerebellar hemorrhage without coincidental-cerebral hemorrhage	10	0.0058

* Read before the Section of Nervous and Mental Diseases at the Eighty-second Annual Session of the American Medical Association, Philadelphia, June 10, 1931.

Case Abstracts. CASE 1.—A-951, male, negro, aged 60 years, admitted to Minneapolis General Hospital August 15, 1909, complaining of a pain on the movement of his right leg and exhibiting evidences of senility. He had been unable to walk for 2 years. Died August 28, 1909. No other clinical data available. *Autopsy:* On section of the cerebellum, in right lobe near the worm, there is a firm grayish-yellow caseated mass which projects toward the right and measures about 1.5 cm. in diameter and 5 cm. in length. This is surrounded by a grayish-white thickened wall and in the middle of the pulp of the right lobe there is a hemorrhagic area containing a thick, dark, firm clot about 2 cm. in diameter. Vessels at base of brain are thickened and tortuous. Microscopic examination shows a large area of necrosis surrounded with thick capsule with connective tissue hyperplasia, dense lymphoid cell infiltration and occasional giant cells. *Comment:* Though available clinical notes are limited, the autopsy findings indicate that clinical course continued over 2 years and that death was not caused directly by the hemorrhagic lesion, which was well encapsulated.

CASE 2.—A-14-234, male, aged 51 years, baggageman at Union Depot, admitted to St. Paul City and County Hospital November 18, 1914. Except for slight cold and pain in back of head, was well until November 11, 1914. Then he became too weak to work. Headache developed and vomiting persisted. On November 16, was found unable to talk; appeared drowsy. Breathing labored at intervals. Did not regain consciousness in the hospital. Examination on November 18, revealed thickening of all palpable arteries. Knee jerks, 2 +; Babinski and ankle clonus, bilateral; Achilles reflex, present on left side only. Exitus November 26, 1914. *Autopsy:* A large blood clot, 2 cm. in diameter, is found in left lobe of cerebellum. Circle of Willis and the other cerebral arteries show marked nodular thickenings. *Comment:* Hemorrhagic focus is illustrated in Fig. 1. Onset with headache localized in occipital region, and vomiting and prostration, without loss of consciousness for the first few days, is quite typical.

CASE 3.—A-17-56, male, aged 73 years, admitted to Minneapolis General Hospital January 15, 1915, with right hemiplegia of spastic type. Clinical note, March 7, 1917: "I feel about all in," said both his legs were jerking. He went to bed. At 11.00 P.M. he began to vomit violently. Did not speak, but could help himself. Fell asleep and this morning was found in stupor. Protrudes tongue slightly. Unable to answer questions. Moans at times, especially when touched. Coughs. Pulse irregular, blood pressure 165 systolic and 108 diastolic. Left pupil slightly larger than the right and slightly irregular in outline. Light reflexes absent. Right eye deviates outward. Right face smoother than left, right corner of mouth somewhat depressed. Right arm and leg very spastic. Right knee jerks rather active, left feeble. Babinski great toe sign positive on right, doubtful on left. Right abdominal reflex absent, left feeble. Wassermann, negative. March 8, 1917, bloody spinal fluid removed under increased pressure. Pulse quite regular, 98, until 8.00 P.M. Breathing became labored and patient died the next day. *Autopsy:* Upon reflecting dura considerable quantity of bloody fluid is found to be present in the pia-arachnoid space. Upon sectioning the brain, all of the ventricles are filled with bloody fluid. There is a large hemorrhagic lesion occupying the center of the cerebellum. *Comment:* Patient presented an old cerebral hemiplegia for which he was receiving custodial care. Onset of cerebellar hemorrhage indicated by violent vomiting. Lesion penetrated cerebellar parenchyma to fourth ventricle within several hours after onset, followed by coma and early death. Signs of former cerebral lesion complicated the neurologic picture.

CASE 4.—A-20-25, male, aged 55 years, admitted to Minneapolis General Hospital January 20, 1920, having been found unconscious. He had always been well previously. He did not regain consciousness at the



FIG. 1.—Circumscribed hemorrhagic lesion, Case 2.



FIG. 2.—Massive hemorrhagic lesion communicating with subarachnoid space, Case 7.

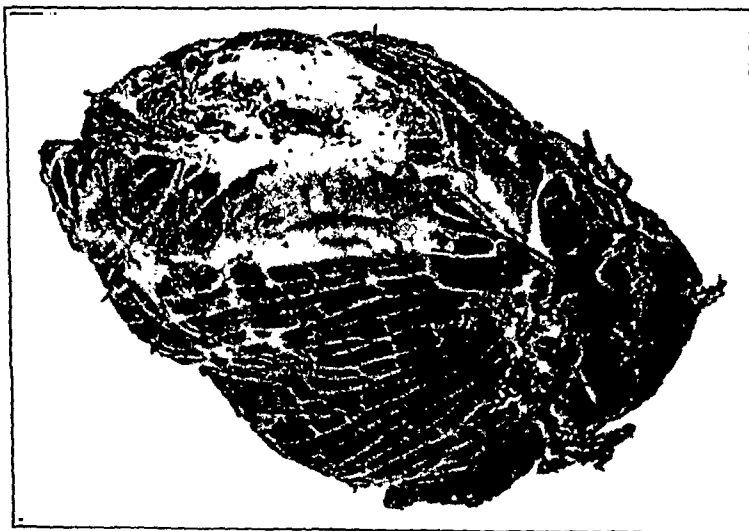


FIG. 3.—Hemorrhagic extravasation to cerebellar cortex, Case 7.



hospital and died 14 hours after admission. *Autopsy:* On removing brain 15 gm. of clotted blood are found escaping from left cerebellar fossa. Sectioning reveals large hemorrhage into left cerebellar lobe with softening of the parenchyma, leaving only a shell, less than 1 cm. in thickness, surrounding the hemorrhage. The blood clot extends into the fourth ventricle. Blood tinged fluid is present in both lateral ventricles. Masses of blood clot are present in anterior horns. Bloodvessels show extensive nodular thickening; the greatest involvement is along the middle cerebral arteries and the circle of Willis. Microscopic examination shows softening and hemorrhage; many eosinophils in parenchyma around hemorrhage. *Comment:* Here we have represented the more fulminating type of syndrome. The lesion, a massive one, allowed no interval to observe cerebellar signs uncomplicated by neighborhood involvement.

CASE 5.—A-20-362, male, aged 60 years. At midday, September 30, 1920, he complained that he felt very sick. In going to his room he fell over a trunk. The housekeeper helped him into bed; patient could use but one arm. At 3.05 the following morning he was found dead. *Autopsy:* There is little blood over the base of the brain which has escaped from a tear in the left lateral cerebellar hemisphere. The central part is occupied by a large blood clot. The hemorrhage communicates with the cavity of the fourth ventricle, filled with blood. Clotted blood found also in the aqueduct of Sylvius and in the third ventricle, and lateral ventricles contained fluid blood. The arteries over the base of the brain show no changes except in the posterior cerebral and cerebellar branches. These contained a large number of yellowish thickened intimal areas. Microscopic examination of organs shows hyalin degeneration in kidneys, spleen, etc. *Comment:* Quite similar to Case 4, except that several hours intervened during which patient was conscious. During this interval the signs of an acute cerebellar attack are suggested by the available record of complaints.

CASE 6.—A-26-1113, male, aged 65 years, merchant, was found dead. He was last seen alive in the afternoon of December 17. It is reported that there had been recent nose bleeds. *Autopsy:* There are blood clots in the subdural space of the left posterianal fossa and some free blood in the subarachnoid space over the base. There is hemorrhage and softening involving the entire central portion of the left cerebellar hemispheres with a tear of 6 cm. in diameter across the free surface. There is marked thickening and beading of all the arteries over the base of the brain. *Comment:* Another illustration of quite sudden death caused by hemorrhage into the cerebellum.

CASE 7.—A-28-223, male, aged 62 years, railroad laborer, admitted to St. Paul City and County Hospital July 6, 1928, complaining of dyspnea, headaches, pain in cardiac region and in his back, swelling of his hands, feet and legs—signs of cardiorenal failure. On afternoon of day following his admission, patient became very restless, severe headache developed and coma set in early that evening; his respirations became very labored and stertorous in character. He died at 1.30 P.M., July 8, 1928. *Autopsy:* There is an area of hemorrhage over one-half the surface of the right lobe of the cerebellum, and on cut section there is found to be a massive hemorrhage in the right lobe of the cerebellum which has destroyed about one-third of the substance, and there is hemorrhage about 2 cm. in diameter in the left lobe of the cerebellum. The cerebral vessels show little evidence of sclerosis. *Comment:* Patient developed first signs of acute cerebellar involvement on the second day in the hospital. Restlessness and headache were followed in 5 hours by coma and early death, probably due to the hemorrhagic penetration through cerebellar cortex. This is illustrated in Fig. 2.

CASE 8.—A-30-45, male, aged 62 years, admitted to Minneapolis General Hospital March 17, 1930. History of high blood pressure for some time.

There had been attacks of indefinite type, supposedly related to high blood pressure, which made him unable to hold his position of night watchman. He rather suddenly complained of heat and rose from his chair, then fell "into a heap." He had not become unconscious. Attempted erect posture several times but failed. He complained of headache, dizziness and vomiting. Heart was enlarged to the left. Blood pressure was 205 systolic and 120 diastolic. Neurologic examination at time of admission revealed pupils equal and normally reactive and a divergent squint. Mouth was pulled very slightly to the left side. Speech was mumbling and slurring. Tongue deviated slightly to the right. Abdominal reflexes were more active on the right side. Muscle power in right arm seemed slightly reduced. No other signs of palsy; no sensory disturbances present. Reflexes presented no other changes. Vertigo persisted. Patient became more drowsy and continued to vomit. Spinal puncture brought forth very bloody fluid under marked increased pressure. Temperature subnormal on admission, but it rose gradually to 103.8° F. prior to death. Blood pressure 180 systolic and 100 diastolic on second day. Pulse range from 70 to 120. Respiration 22, gradually rose to 32. Totally unconscious on 5th day, died on the following day. *Autopsy:* Lateral and third ventricles markedly distended. Right caudate nucleus presents a small pigmented cyst $\frac{1}{2}$ cc. in diameter. The cerebellum is greatly softened and enlarged. It is pressed firmly against the aqueduct of Sylvius and causes apparently complete collapse of the aqueduct. Section through the cerebellum reveals large hemorrhage occupying most of the right lobe and about one third of the left lobe. There is a small amount of blood beneath the arachnoid in its inferior surface. The vessels at the base of the brain show no gross evidence of disease, although some in the peripheral areas are moderately atheromatous. *Comment:* Clinical course was sufficiently protracted to portray a fairly typical cerebellar syndrome. Brunt of lesion suffered by right lobe, but vermis and part of left lobe became involved, presumably by fairly rapid extension. The penetration through cerebellar cortex and pressure of the tumorous mass toward the brain stem explain the early fatal termination.

CASE 9.—A-30-735, 1 month old, patient of Dr. M. J. Lynch, born at St. Mary's Hospital. Delivery normal. Nothing of note until the 10th day, then began projectile vomiting and loss in weight. Child vomited after nearly every feeding for the following 3 days. At first vomiting was projectile in character. *Autopsy:* The right lobe of the cerebellum is larger than the left, pushing the tentorium upward. The lateral ventricles are markedly distended with fluid. Cut section of the cerebellum shows a large clot of blood in the right lobe with softening in the adjacent areas. Other postmortem findings: (1) internal hydrocephalus; (2) terminal bronchopneumonia. *Comment:* Though meningeal bleeding in the posterior fossa is relatively frequent in the newborn, massive hemorrhage into the cerebellum is decidedly rare. In this case of an infant, projectile vomiting began on the 10th day, prior to which date attending physician had noted nothing irregular. Signs of increasing intracranial pressure were evident, producing death 3 weeks after onset of first symptoms of cerebellar attack. No developmental anomaly could be established.

CASE 10.—A-30-1252, female, aged 42 years, admitted to Minneapolis General Hospital August 22, 1930, in coma with Cheyne-Stokes respiration. The day previously patient began to complain of headache. She gradually became weaker and comatose 2.00 A.M. the following morning. Pupils pin point, did not react to light. Heart enlarged to left, systolic murmur heard at apex. Neurologic examination revealed palsy in right arm and leg. She expired at 11.20 the morning of the same day. *Autopsy:* Brain reveals an area of recent hemorrhage and softening, 2 cm. in diameter, in

the left lateral lobe of cerebellum, involving the area of the dentate nucleus. No degeneration in the cerebral arteries. *Comment:* Pathogenesis not determined. Nothing of a neoplastic character or developmental anomaly was noted.

TABLE 2.—COMPOSITE SUMMARY OF CASES 1 TO 10, SHOWING AGE, SEX, DURATION, LOCATION AND EXTENT OF HEMORRHAGE, AND STATE OF BLOODVESSELS.

Age.	Sex.	Duration.	Area chiefly involved.	Extent of hemorrhage.	Degeneration of cerebral vessels.
(1) 60	M.	2 (?) yrs.	Right lobe	Circumscribed	Yes
(2) 51	M.	15 days	Left lobe	Circumscribed	Yes
(3) 73	M.	3 days	Vermis and both lobes	Into ventricular system	Yes
(4) 55	M.	14 hours	Left lobe	Into ventricular system	Yes
(5) 57	M.	15 hours	Left lobe	Into ventricular system	Yes
(6) 65	M.	Found dead	Vermis and both lobes	Into subdural space	Yes
(7) 62	M.	1 day	Both lobes	Into subdural space	Slight
(8) 62	M.	6 days	Right mainly, vermis and left also	Into subdural space	Yes
(9) 1 mo.	M.	20 days	Right lobe	Circumscribed	No
(10) 42	F.	1 day	Left lobe	Circumscribed	No

Historical. Sedillot¹ of Paris, France, was the first to report a case of cerebellar hemorrhage in 1813. Huss reported the first case in Sweden in 1842; Dunn in the British Isles, 1849; Schulz in Germany, 1854; and de Nasca in Italy, 1863. Childs² is the first American author. His case was that of a girl, aged 19 years, whose symptoms developed while amusing a child by shaking her head violently. Carion³ published a report of 7 cases of hemorrhage, and 1 of softening; he referred to previous publications by well known 19th century French neurologists: Andral, Hilliaret, Brown-Sequard, Ollivier, Raymond and others. His clinical observations were remarkably comprehensive and precise. Mills⁴ demonstrated a brain presenting hemorrhage in the cerebellum, and by extension into the ventricular system, at a meeting of the Pathological Society of Philadelphia in 1889. Starr⁵ could find in the literature up to that time 27 cases diagnosed postmortem. While arteriosclerosis was recognized as a predisposing factor by early authors, other etiologic factors as trauma, epileptiform seizure, syphilis, diabetes, aneurysm and acute infection, referred to below, were made clearer in more recent times. However, the literature shows a notable paucity of reports concerning apoplectiform cerebellar disease. This applies even more to thrombosis than to hemorrhage. Though relatively small foci of softening are not infrequently encountered in postmortem examinations, the more massive and isolated thrombotic lesion producing the unique clinical syndrome of cerebellar

involvement followed by death is still more uncommon than isolated hemorrhage.*

Symptomatology. Three types of syndromes characterize the symptomatology and course: (1) Fulminating; (2) grave; (3) benign.

In the first type there are no premonitory signs or, at the most, patient utters a brief cry and places his hand at the nape of the neck. He falls over and death is practically instantaneous. Some patients are found dead. In the present series of cases reported there was but one belonging to the fulminating type.

Cases of the second type have an onset less abrupt. Premonitory symptoms are frequently determinable. These are severe occipital pain, sensation of turning, nausea, vomiting, increasing feeling of prostration and inability to stand upright, irregularity of pulse, labored breathing and rotation of the head away from the side of lesion. Pupils are contracted and fixed. Rigidity of neck and Kernig's sign may be present.⁶ Location and extent of the hemorrhagic lesion are not uniform, hence the rapidity and degree of development of symptoms vary. Impairment of consciousness may be noted within a few minutes or may not be present until some hours or more later. Sometimes relatively early drowsiness is followed by lucidity until terminal coma sets in. Spinal puncture yields a bloody fluid. Inasmuch as the brunt of the lesion is more often confined to one lobe, it is possible to make out, in patients who are able to coöperate, the syndrome of unilateral localization. In addition to signs of dyssynergia involving arm and leg of the side of the lesion, one notes in some cases a dysarthria, and nystagmus is present as a rule. Divergent squint is frequently observed. Asynergia, nystagmus and vertigo have the tendency to persist while the patient is conscious. Signs of pyramidal tract involvement are notably absent. Tonic or clonic convulsive attacks occur infrequently. Labored breathing, irregular and rapid pulse, rise in temperature and coma precede exitus.

In cases of the benign type we find the premonitory signs mentioned above less constant and less pronounced. Quite likely, a goodly number of these cases are undetected antemortem. If the expected circumscribed lesion is relatively small, the cerebellar symptoms are minimal. The larger lesion produces signs of increasing tumor in the posterior fossa ending in early death.

In reviewing the symptoms we can note that the fulminating syndrome offers practically nothing characteristic of the cerebellum itself, nor even of the posterior fossa. Antemortem localization is practically impossible in all these cases.

Referring to the second or grave syndrome, a variable train of

* Following the writing of this report I had a case of cerebellomalacia without major signs of brain stem or cerebral lesion which came to autopsy at St. Mary's Hospital.

symptoms become manifest to the clinician. Posterior fossa insult is clearly indicated. Headache, vertigo and asthenia at the time of onset are attributable to initial circulatory disturbance. Irregularity of pulse and respiration signify neighborhood medullary involvement. Nystagmus and deviation of the eyes suggest an irritative or destructive process in the roof nuclei or vestibular fiber tracts. Rigidity of the neck and Kernig's sign, if present, point to menigeal irritation. Loss of power in individual muscle groups and objective sensory disturbances indicate, if present, neighboring brain stem involvement. Focalized cerebellar involvement is shown by impairment of the fundamental cerebellar function: synergia, defined as "the power by which movements more or less complex, but functionally definite, are associated in special acts."⁷

Disturbances of equilibrium, incoördination, dysdiodochokinesia, dysmetria, lateral nystagmus, dysarthria, turning of head away from the affected side, noted in some cases of cerebellar hemorrhage, belong to the asynergic category. In the grave type the vermis does not escape involvement. Extracerebellar signs are, after all, prominent. Many of the premonitory signs point to neighboring posterior fossa structures, whereas the late signs include those of irritation and distention of the ventricular and subdural cavities. McCollum⁸ calls attention to hyperglycemia as a possible symptom of grave cerebellar hemorrhage.

The benign type tends rather to offer a possible recognition of the so-called pure cerebellar syndrome. Here a varying picture of dyssynergia, uncomplicated by neighborhood signs, tends to obtain, for the hemorrhagic lesion is small and circumscribed. Impairment of synergia persists in these cases. This persisting impairment is suggested in Case 1. It is indicated in Schaller's case.⁹

Pathogenesis. Bloodvessel disease is the common primary factor. Arteriosclerosis with hypertension is found in a majority of the cases. Syphilitic arteritis is not infrequently accountable. Diabetes may explain a hemorrhagic lesion in the cerebellum in young persons.¹⁰ Birth trauma producing a rupture of the tentorium cerebelli near the anterior extremity of the strait sinus is followed by cerebellar venous hemorrhage. This instance is suggested in Case 9. Postnatal traumatic hemorrhage caused by direct injury to the cerebellum is extremely rare. An illustration of hemorrhage into cystic cavity following head trauma is indicated in Hird's case.¹¹ André-Thomas¹² reported 2 cases of hemorrhage following head injury. There were no others in a series of 4076 head wounds observed during the World War. There have been but few cases resulting from injury sustained in boxing and in violent exercising, *e. g.*, the case of Hoffman.¹³ Aneurysmal hemorrhage is also most rare; Hamilton¹⁴ found 4 in a series of 86 cerebral aneurysms. Acute arteritis developing in the course of an acute infectious dis-

ease is known to have produced cerebellar hemorrhage. Epileptiform seizure figured in a patient without arterial disease, in the case reported by Thyne¹⁵ and was followed by the grave type of cerebellar hemorrhage. Alcoholism and epilepsy were associated in Boldt's case.¹⁶

An explanation for the rare incidence of cerebellar hemorrhage is suggested by the liberal anastomosis of bloodvessels of both sides in the median of vermis; this area is most rarely the focus of vessel rupture. Lacunar disintegration, while relatively common in the senile cerebrum, is much less pronounced in the cerebellum. The artery to the dentate nucleus resembles the lenticulostriate artery of the cerebrum in that it is as a rule involved in cerebellar hemorrhage; this artery is a branch of the external branch of the superior cerebellar artery. Multiple hemorrhagic areas have been noted. A small and relatively benign hemorrhagic focus or softening may, of course, be followed after an interval by a severe hemorrhage.

Syndrome of Cerebellar Apoplexy. It is apparent from the foregoing that it is not possible to define one syndrome which will characterize all cases. As a general rule it can be stated that in those cases where recognition of identifying symptoms and signs is impossible, the course is brief and fulminating. In the absence of coma, correct antemortem diagnosis is possible.

Premonitory signs: severe occipital pain, sensation of turning, nausea, vomiting and feeling of intense prostration, point to cerebellar localization. Signs pointing to the nonequilibratory, as well as to the equilibratory dyssynergias, are typical. The absence of sensory and pyramidomotor involvement, and retention of mental integrity at time of onset, is characteristic.

Summary. 1. Postmortem findings and clinical notes of 10 cases of hemorrhage into the cerebellum only are reported.

2. The history, symptomatology and pathogenesis of the condition are discussed.

3. Postmortem statistics indicate an extremely low incidence rate for isolated cerebellar hemorrhage, and even more so for thrombosis.

4. Clinical syndromes of cerebellar apoplexy are described and diagnostic criteria outlined.

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SPONTANEOUS BILATERAL PNEUMOTHORAX.

WITH REPORT OF A CASE AND REVIEW OF LITERATURE.

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SPONTANEOUS bilateral pneumothorax is very rarely observed, although probably it occurs more frequently than is reported. Generally, it is a complication of evolutive pulmonary tuberculosis, though it may follow several other conditions. Less than 50 cases have been reported in the literature.

Owing to the rarity of spontaneous bilateral pneumothorax and to the fact that American literature on this subject is rather meager, it should be of interest to report the following case to which is appended a short summary of the literature with bibliography.

Case Report. On July 16, 1929, Dr. R. S. Breakey, Monticello, N. Y., referred to the Loomis Sanatorium a white man, aged 27 years, for consultation regarding a pneumothorax involving his left hemithorax. About the end of June, 1929, he developed a common cold while in the pursuit of his occupation as traveling salesman. The symptoms were pharyngeal irritation, slight nasal catarrh and later a rather irritating cough with slight frothy expectoration. There was no sudden pain nor feeling of weakness, faintness, dyspnea nor tightness in the chest. His appetite was good; he did not feel feverish nor unduly fatigued. He remained active, but his symptoms gradually got worse; his cough and expectoration increased and the latter became quite "phlegmy" in character; fatigue became more noticeable and in the evening he felt flushed and feverish. On June 28, 1929, he went to bed and called in a doctor, who found his temperature 102° F. (mouth). After a week of bed rest his temperature became normal and cough and expectoration diminished. On July 6, 1929, he first became conscious of a dull pain in his left midchest anteriorly. The pain was aggra-

vated on deep breathing but was not accompanied by conscious dyspnea. He was in bed at the time and does not recall any undue strain. Dr. Breakey suspected spontaneous pneumothorax and a Roentgen ray examination established the diagnosis. Between June 25 and July 16, 1929, he lost about 10 pounds in body weight. At the time of examination on July 16, 1929, he felt fair; appetite and digestion were good and he slept well. He had cough and a moderate amount of muco-purulent sputum. He was not dyspneic. He had a dull pain over the left anterior midchest which was aggravated on movement, but not on deep breathing.

Of interest in his past history was an undue susceptibility to colds dating from childhood. The symptoms were cough and expectoration, malaise and slight fever; never any blood spitting. Since 1926 these attacks were accompanied by pain in the chest. The pains were not very severe and were of a dull, rather than of a sharp stabbing character, and localized over the upper anterior quarter of both lungs; during a given attack the pain was chiefly unilateral, but the same side was not always involved and he could not say which side was more frequently affected. In 1924 he had influenza; the symptoms were fever (maximum 103° F., mouth), malaise, general aching over the body, cough and expectoration, but no hemoptysis. He was in bed 3 or 4 weeks and convalescent for a month. There was no history of allergic diseases. He married in February, 1924; his wife is in good health; there are no children.

Physical examination showed a moderately undernourished and frail-looking man (weight 54.6 kg.—standard weight 73.9 kg.), slightly stooped, rather nervous apprehensive look, breathing easily. His fingers were slightly clubbed and the nails showed longitudinal striations but no pitting of the nail beds. The thorax was long and slender and movement on the left side was less than on the right. There was no bulging and the only visible pulsation was in the left fifth interspace internal to the nipple line.

Over the right lung the percussion note was of good quality. Breath sounds were slightly exaggerated throughout. Below the eighth spine, extending to the posterior axillary line at the tenth spine, there were fine and medium râles following cough. Over the left lung the percussion note was hyperresonant throughout, more so in the axilla. Breath sounds were diminished to suppressed throughout, anteriorly; audible, but diminished throughout, posteriorly. There was no succussion splash or shifting dullness, metallic tinkle or coin sound. There were no râles.

His teeth and gums were in good condition. The pharynx was injected. The right naris showed slight hypertrophy of the middle turbinate and slight deviation of the septum to this side. The left middle turbinate was moderately hypertrophied. He had no sense of smell. In the larynx the true cords were uniformly pink to red in color. There was no ulceration or destruction of tissue. The changes amounted to slight catarrhal laryngitis.

The apex beat was in the fifth interspace, 7 cm. from the midsternal line. The organ as a whole was slightly displaced to the right. The pulse was regular in force and tension, but of small volume. The blood pressure was systolic, 100; diastolic, 68. Physical examination was otherwise negative.

Fluoroscopic examination revealed the left lung to be about 50 per cent collapsed and there was a very small amount of fluid in the costophrenic sulcus. The heart and mediastinum were slightly displaced to the right, particularly on expiration. There was no evidence of gross parenchymal lung changes.

Stereoscopic roentgen ray films of the chest showed in the right lung that the markings throughout were intensified; the descending trunks were heavily studded; the mediastinum and heart were slightly deviated to this side. On the left side there was a hydropneumothorax with a very small

amount of fluid in the costophrenic sulcus; the lung was about 50 per cent collapsed, free of adhesions, and there was no evidence of cavity or gross pathology in it.

He had 20 cc. of muco-purulent sputum in 24 hours. Tubercle bacilli could not be demonstrated in it either on direct smear or after digestion and concentration. Seven cubic centimeters of digested sediment from 45 cc. of sputum were injected into a guinea pig on July 18, 1929. The animal was killed on October 22, 1929, and at the postmortem examination there was no evidence of tuberculosis. The Kahn test and tuberculosis complement fixation were negative.

The patient was kept at bed rest except for bathroom privileges. The râles audible on admission over the base of the right lung cleared up within the first 2 weeks. During sanatorium residence the temperature range was within normal limits. At each weekly fluoroscopic examination progressive reexpansion of the lung was noticed. On August 13, 1929, the pneumothorax space was limited to the area above the second rib.

On August 16, 1929, he noticed he was unusually dyspneic and complained of a feeling of fullness in the chest. These symptoms appeared without apparent cause and he had not consciously strained or exerted himself in any way. This called for fluoroscopic examination which showed the right lung to be about 80 per cent collapsed and a small amount of fluid in the sulcus. Attention was focused on the collapse rather than the side, and it was presumed it was still the left lung that was involved. Subsequent events showed that this was probably an error, because on physical examination on August 29, 1929, signs of pneumothorax were found over the right side and the only abnormality over the left chest was exaggerated breath sounds. On fluoroscopic examination a right-sided pneumothorax was demonstrated with the lung about 60 per cent collapsed and a small amount of fluid in the sulcus. Roentgen ray examination on August 30, 1929, showed a hydropneumothorax with the lung 50 per cent collapsed and apparently free of adhesions. There was a very small amount of fluid in the costophrenic sulcus. There was no significant change in the parenchyma of the partially collapsed lung and no evidence of cavity. The diaphragm was slightly depressed and the heart and mediastinum just a little displaced to the left. The left lung showed a pneumothorax with a very tiny amount of air overlying the apex. This would probably be overlooked without knowledge of the previous films. The patient was kept at strict bed rest and fluoroscoped once a week, being transported to the fluoroscope some 20 yards away from his room on a stretcher. Twenty cubic centimeters of fluid, which was practically all that was present, were aspirated from the right costophrenic sulcus. It was yellow in color and slightly purulent. Examination of smears by Ziehl-Neelson and Gram methods were negative. Cytologic examination revealed some polymorphonuclears. Culture on dextrose broth was negative after 48 hours. It was cultured on potato and potato-egg media, but negative for tubercle bacilli. On September 3, 1929, 6 cc. of the untreated fluid were inoculated into a guinea pig. The pig was killed on November 16, 1929, and at the post-mortem examination there was no evidence of tuberculosis.

Reexpansion took place gradually and on September 30, 1929, fluoroscopic and Roentgen ray examinations showed both lungs were completely re-expanded and there was no evidence of gross pathology in them. The patient was allowed to sit up and by easy steps worked up to increased exercise. At the time of his discharge on October 20, 1929, he was leading a normal life and apparently well. In response to a questionnaire, he replied on November 6, 1930, that he was in good health and working full time since leaving the sanatorium.

Comment. The absence of evidence of clinical pulmonary tuberculosis on physical and Roentgen ray examinations, together with

failure to demonstrate tubercle bacilli in the sputum or pleural fluid on smear, culture or animal inoculation, rules out tuberculosis as an etiologic factor in this case. As there was no obvious cause for the collapse it must be classified as benign or idiopathic pneumothorax.

Discussion of Literature. The etiology of spontaneous (idiopathic) pneumothorax is still very obscure. It may occur without any immediate appreciative cause or in the course of a more or less violent effort in a patient up to then apparently well. The gaseous effusion in the pleural cavity may dissipate rapidly without any complications or sequelæ or, rather exceptionally, it may provoke a slight pleural exudate (as in the author's case) which is usually absorbed. The condition, however, is not always benign when non-tuberculous; in an occasional case there may be much pain, dyspnea and syncope with a fatal termination.

Spontaneous bilateral pneumothorax is mostly a sequel of evolutive pulmonary tuberculosis. It is said that about 58 per cent of the cases are of this type. It may also be a sequel of well characterized emphysema and about 16 per cent answer to this type. Some cases apparently arise as a complication of traumatism and a few in association with cancer metastases.

Hainaux,¹ in his thesis (1913), collected 14 cases from the French and German literature of fatally terminating spontaneous bilateral pneumothorax as complications of evolutive pulmonary tuberculosis. The cases reported by Meyer,² Marshank,³ Gray⁴ and Bourne⁵ were of this type also and terminated fatally. Hazen's⁶ patient recovered.

The cases of Recamier,⁷ Hayashi⁸ and Massini and Schönberg⁹ were complications of emphysema and ended fatally. Emerson's¹⁰ fatal case followed asthma.

Elte,¹¹ Leclerc,¹² West,¹³ Goodhart,¹⁴ Hawes,¹⁵ Mills,¹⁶ and Atwood¹⁷ reported cases of spontaneous bilateral pneumothorax following traumatism with recovery. Benedict¹⁸ reported 3 cases with recovery.

The cases of Briggs,¹⁹ Fleischmann,²⁰ Radek²¹ and Borchard²² were associated apparently with cancer metastases and ended fatally.

Olbrechts²³ distinguishes between simultaneous and successive spontaneous bilateral pneumothorax. By simultaneous spontaneous bilateral pneumothorax he designates an entrance of air into both pleural cavities either at the same time or into the second cavity before the pneumothorax in the first is absorbed. The first eventuality Olbrechts says is extremely rare; he could find no categorical example of it reported in the literature, at least as far as concerned bilateral pneumothorax neither attributable to tuberculosis nor traumatism. By successive spontaneous pneumothorax Olbrechts indicates a spontaneous pneumothorax which occurs first on one side and then, later, the occurrence of a spontaneous pneumothorax on the other side. If the second pneumothorax occurs very

soon after the first *and while the latter is still unabsorbed*, it is a spontaneous bilateral pneumothorax. It is impossible to tell, when a patient presents himself with a bilateral pneumothorax, whether both occurred at the same moment or whether they were immediately successive. In the absence of absolute proof such a case must be considered as one of spontaneous bilateral pneumothorax. Sometimes there is an alternating recurrence of the pneumothorax in one pleural cavity or the other. Sometimes the interval between the successive appearances is very long. In Attwood's¹⁷ case a man showed a left spontaneous pneumothorax at the age of 37 years and, 23 years later, developed a right spontaneous pneumothorax. Olbrechts mentions 2 cases, reported personally to him by colleagues Dr. Pauporté and Dr. C . . . (*sic*), in which the interval between the right and left spontaneous pneumothoraces was 3 years in each case. In both of these cases the original unilateral pneumothorax appears to have developed following a bronchopneumonia.

Simultaneous spontaneous bilateral pneumothorax is uncommon and most likely to be met with in traumatic cases. In Elte's case a young man developed a right spontaneous pneumothorax following a traumatism. Two days later he developed a left spontaneous pneumothorax. There was no evidence of tuberculosis. He made a rapid recovery. The case of LeWald²⁴ was of the same type, the second pneumothorax appearing 8 days following the first, which was accentuated at this time.

The great majority of cases of spontaneous bilateral pneumothorax are, however, of the successive type. Watson and Robertson's²⁵ 2 cases are more or less typical of this type. In the first case, that of a young man, aged 23 years, the condition was seen to be a spontaneous left pneumothorax. This was followed 6 months later by crises due sometimes to a right and sometimes to a left spontaneous pneumothorax. This condition of alternating left and right pneumothorax continued for some years with an apparent recovery. There was neither clinical nor radiologic evidence of tuberculosis. In the second case a young man developed symptoms of right pain and dyspnea. Radiography showed a total right spontaneous pneumothorax. A month later radiography disclosed a partial left pneumothorax. There was no evidence of tuberculosis. Grashey's²⁶ case was much the same.

Most of the traumatic cases are of the same kind. In Leclerc's¹² case a young man developed a left pneumothorax 3 weeks after a traumatism. A right pneumothorax developed 2 months later. The man made a rapid recovery.

Wilson²⁷ reported a case of successive spontaneous bilateral pneumothorax with a month's interval between the pneumothoraces on the two sides. There was no evidence of tuberculosis. The man recovered.

A few very unusual cases should be mentioned. In Bourne's⁵ case the patient was an infant. Bilateral pneumothorax was found

at autopsy resulting from a miliary tuberculosis. In Scheltema's²⁸ case the patient was a child, aged 7 weeks, who, since birth, showed respiratory difficulty. Examination showed congenital deformities of the left hemithorax; heart displaced to the right; left diaphragm depressed, and bilateral pneumothorax. The condition suggested agenesis or aplasia of the lungs.

Little need be said regarding the etiology of spontaneous bilateral pneumothorax, as there is no definite agreement concerning it. Many consider that the rupture of a superficial tubercle is the cause of the lung rupture, but the absence of evidence of clinical tuberculosis and the significant fact that in the literature there has been no case recorded of this type in which pulmonary tuberculosis subsequently developed, is strong evidence against this view. In our own case the history of repeated colds and chest pains suggests the probability of a bilateral localized emphysema, although it could not be demonstrated clinically.

LeWald has advanced the theory that bilateralism of pneumothorax may occur from the passage of air from the right to the left pleural cavity across an orifice of the mediastinum. Fistulization of the mediastinum in the course of therapeutic pneumothorax has been reported and perforation of the mediastinum may probably occur when tuberculous ulcerations exist, but outside of such cases it seems hard to believe that LeWald's suggestion could be substantiated, more especially in nontuberculous cases. Bedford and Joules²⁹ reported a nontuberculous case (much like my own, except that there was no history whatever of any preceding disease) with recovery. They also suggest the possibility of leakage through the mediastinum or possibly some communication between the two pleural cavities.

The same may be said in regard to the theory of vicarious emphysema put forward by Elte.

Olbrechts thinks that it is more logical to admit that the bilateral pleuropulmonary rupture, when it is not the result of a simple coincidence, depends upon an anatomic disposition either congenital or acquired, which entrains a more or less marked fragility to the surface of the lungs.

Consideration of the literature suggests that cases of spontaneous bilateral pneumothorax associated with pulmonary tuberculosis usually end fatally. The association with emphysema or asthma is not necessary fatal and some of these patients recover. Patients developing bilateral pneumothorax following traumatism and the so-called idiopathic cases usually completely recover. In general, the prognosis is favorable in nontuberculous spontaneous bilateral pneumothorax. In Meyer's patient spontaneous collapse took place on four occasions, each following the exertion of the coitus and the last one proved fatal.

Conclusion. A case of benign or idiopathic bilateral pneumothorax with recovery is reported, the rupture of the second lung



FIG. 1.—July 23, 1929. Spontaneous pneumothorax on the left with a small amount of fluid in the costophrenic sulcus. Right lung clear.

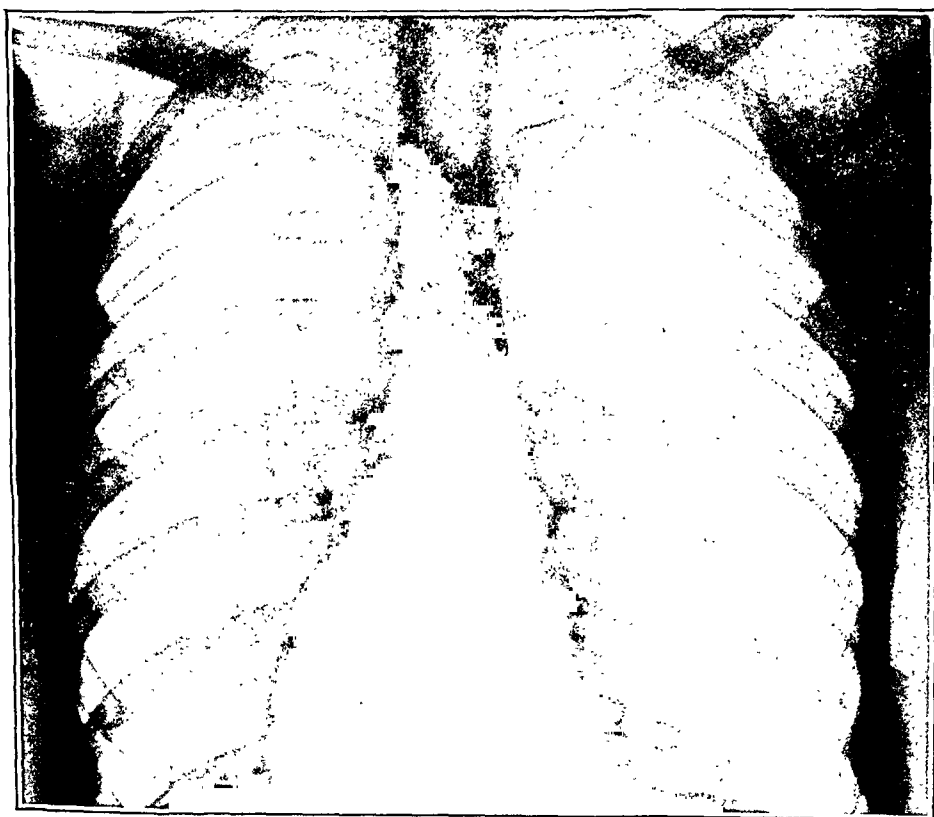


FIG. 2.—August 30, 1929. Spontaneous pneumothorax on the right side with fluid in the costophrenic sulcus. Reexpansion of the left lung is incomplete.



FIG. 3.—September 30, 1929. Both lungs fully reexpanded and apparently clear.

taking place before the complete reëxpansion of the first so affected. The case may, therefore, be classed as simultaneous spontaneous bilateral pneumothorax according to Olbrechts' classification.

The literature of the subject is reviewed.

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RESPIRATORY MEASUREMENTS AS AFFECTED BY SMOKING AND BY ATHLETICS.

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DESPITE the widespread use of tobacco there is very little accurate information concerning its effects on the human organism. The pharmacologic actions of nicotine are well known but data as to whether chronic smoking changes the functions of the smoker are extremely few. There is no doubt that a person who is unaccustomed to tobacco may suffer unpleasant effects from his first indulgence. Certain authors (Dixon¹) state that smoking may cause hyperacidity, and others believe this habit to be an important predisposing cause of peptic ulcer (Moynihan,² Harris.³) Other writers stress the importance of tobacco as a cause of palpitation and cardiac arrhythmias (Williamson,⁴ Poulsen,⁵ Sollman,⁶ Dixon¹.) Tobacco has been stated to be a cause of angina pectoris. Moschcowitz⁷ has reported 4 cases in which it seemed likely that such was the case. On the other hand Johnson,⁸ who studied a fairly large series of cases, stated: "It is doubtful whether tobacco plays a major rôle in the etiology of angina pectoris." Johnson failed to note any difference in the blood pressure of smokers and abstainers. He believed that the chief effect of smoking was local, on the pharynx.

There seems to be a general impression that smoking "hurts the wind." Most athletic coaches and trainers forbid tobacco. So far as we know, comparative observations on the ventilation of smokers and abstainers have not been made. We have undertaken such studies with the idea of determining whether persons who smoke excessively are more short-winded than individuals who do not smoke.

Method. In a previous publication⁹ a method of expressing dyspnea quantitatively has been described. This method depended on the general principle that an individual begins to feel short of breath when his actual ventilation becomes more than a certain fraction of his maximum ventilation. (In subjects with respiratory obstruction this principle is not valid.) The actual ventilation can be readily measured and the maximum ventilation in any given time is obviously proportional to the maximum ventilation for one breath, or in other words, to the vital capacity. In accordance with this principle it was shown in a series of measurements on normal subjects and on patients during various degrees of exertion, that the

degree of respiratory distress was proportional to the expression $\frac{\text{ventilation}}{\text{vital capacity}}$. It was shown also that obese individuals had higher

and thin subjects lower values for this quotient than did individuals of average nutritional state. In order to "correct" the values for such variations in weight it was necessary to have a "weight factor." It was shown by studies on groups of normal individuals of different physical makeup that the following formula was adequate for this purpose:

$$\frac{\text{Ventilation}}{\text{Vital capacity}} \times \frac{1 + \frac{\text{Ideal weight}}{\text{Actual weight}}}{2}$$

For the sake of simplicity the value arrived at by the above formula was called the Ventilation Index.

The exercise consisted of walking up, across and down from a platform 2 steps high at a given rate of speed for 2 minutes, the expired air being collected during the time and during the subsequent 5 minutes. In the original study observations were made on the ventilation during and after 4 different degrees of exertion, these consisting respectively of 6 (Exercise I), 12 (Exercise II), 16 (Exercise III) and 24 (Exercise IV) "round trips" in the 2-minute exercise. In the present study observations were made only of the second and fourth of these exercises, the former rather mild and about equal to walking at an ordinary pace, the latter being approximately equivalent to a slow run. Further details of the method are given in the paper⁹ to which reference has been made.

It is evident from this description that the values for the ventilation index are entirely arbitrary in the sense that a selected exercise is performed for a given time.

The subjects studied consisted of 75 healthy medical students. Forty-two of them did not smoke. The other 33 subjects were heavy smokers in that they all smoked 20 or more cigarettes daily. Observations on occasional and moderate smokers were not made as it was felt that such studies would be difficult of interpretation.

It soon became apparent that the degree of muscular training and the individual's status as an athlete or sedentary person made a marked difference in the results. Consequently, the 2 main groups, smokers and abstainers, were subdivided into sedentary, moderately athletic and very athletic subjects. Such a classification could at best be very rough. The criteria selected were as follows: An individual who had never attempted to "make a varsity team" and who took no regular exercise was classified as sedentary. Subjects who had played on a varsity athletic team and who had continued to take fairly regular exercise in some form were classified as very athletic. Individuals whose athletic activities had been intermediate between those of these groups were considered as "moderately" athletic.

Furthermore, in order to obtain observations in a group of subjects in active "training," measurements were made on 13 members of the football squad of Vanderbilt University. These measurements were made during the football season when the men were in their best possible physical condition.

Results. A. *Comparison of the results in smokers and abstainers.* The 33 subjects who smoked were divided as follows: sedentary, 18; moderately athletic, 11 and very athletic, 4. The 42 individuals who did not smoke included 23 sedentary persons, 14 moderately athletic subjects and 5 very athletic students. Therefore, the 2 main groups—smokers and nonsmokers—were quite comparable as regards the distribution of the sub-groups.

It should be noted that the term "sedentary" as applied to the least athletic of the medical students is used in a purely relative sense. As compared to the average adult they would have to be considered as moderately athletic. Thus even the sedentary students were definitely superior in respiratory measurements to the group of normals studied by Harrison, Turley, Calhoun and Jones.⁹

The average height of the smokers was 68.4 inches; of the abstainers 69.3 inches. The average weights were 150.6 pounds and 149.6 pounds, respectively. It is evident therefore that the abstainers were, as a group, slightly taller and somewhat thinner than the smokers, although the difference was not striking. Average surface area was 1.81 and 1.82 for the 2 groups.

The respiratory measurements are given in Table 1. The average vital capacity was 2.67 liters per square meter in the smokers and 2.64 liters per square meter in the abstainers. Lowest and highest vital capacities were 1.94 and 3.37 for the smokers and 2.08 and 3.20 for the nonsmokers. It seems evident from these data that smoking has no effect on the vital capacity.

The average ventilation per square meter of the smokers was 43.3 and 70.6 for the milder and severer exercises. The corresponding values for the abstainers were 42.0 and 67.4 liters, respectively. In view of the very wide differences within a single group (Table 1) these small differences in the average cannot be regarded as significant.

Values for the ventilation index were also almost the same in the 2 groups. Averages were, for the smokers, 16.9 for the milder exercise and 27.4 for the severer exertion. The corresponding figures for the abstainers were 16.7 and 26.8. Again, the slight difference is in favor of the abstainers, but again, the differences are too small to be significant.

B. *Comparison of the results in sedentary and in athletic individuals.* Comparison of the various sub-groups in Table 1 shows that athletic individuals tend, as would be expected, to have a higher vital capacity, a lower ventilation per square meter for a given exercise, and a

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TABLE 1.

SECTION OF RESPIRATORY

SECTION OF RESPIRATORY

lower ventilation index than do sedentary individuals. The differences in favor of athletes are scarcely large enough to be significant for the mild exercise but are more pronounced for the severer exercise.

The average values for 13 members of the Vanderbilt University football team are shown in Table 2. For the sake of comparison the average values for the sedentary individuals (both smokers and abstainers) of Table 1, are also included. It can be seen that the average vital capacity of the football players was only about 5 per cent greater than that of the sedentary students. For the milder exercise the football players had slightly greater ventilation per unit of body surface than did the nonathletic controls. For the severe exercise the ventilation was considerably (about 8 per cent) less than that of the sedentary individuals. The ventilation index of the athletes was about 5 per cent lower for the milder exertion and about 20 per cent lower for the severer exercise than were the corresponding values for the sedentary students. It is evident that individuals in good "training" breathe considerably more efficiently with unusual exertion than do untrained subjects but that they are not much more efficient in the performance of mild exertion.

A comparison was made between the value to the team of the different football players with the respiratory measurements but it was soon seen that no correlation existed. Two of the players with the highest (poorest) ventilation indices were "stars" and several individuals with the lowest (best) ventilation indices were "scrubs." It is evident that in a group of individuals, all of whom have an excellent physique, the "stars" are not necessarily the men with the best "wind."

The "very athletic" medical students, who were all in excellent physical condition and all of whom took regular exercise, but none of whom were highly trained in the same sense that the football players were, had according to the respiratory measurements, just as good "wind" as did the football players. This finding was rather surprising. Possibly, the latter group would have been superior had the subjects been tested with violent or maximal exertion.

Discussion.—From the above data one might be tempted to conclude that smoking does not affect the "wind" at all. However, such a conclusion seems to us to be unjustifiable for the following reasons:

1. The subjects, being young, had been smoking for relatively few years. It is conceivable that studies on a group of individuals who had been heavy smokers for 20 or more years might show difference from a control group.

2. It is also possible that if a maximal or violent test exercise had been used the smokers would have shown themselves less efficient than the abstainers.

The data do seem to justify the following conclusion: Smoking

for a few years, even to excess, produces no significant decrease in the respiratory efficiency in response to such exertion as is necessitated by the ordinary duties of life.

The data concerning athletes were of interest. For mild exercise the athletes were only slightly more efficient than the sedentary students, but for severe exercise which was in no sense maximal, the football players were about 20 per cent more efficient than the sedentary students. Of special interest is the fact that those medical students who had participated in intercollegiate sports some years before and who had continued to take some form of regular exercise, but who were not in active training at the time the tests were made, were just as efficient in their breathing as were the football players who were highly trained at the time the tests were made.

It appears that once an excellent physical status has been attained, one is able to keep in this condition, for a number of years at least, by relatively mild exercise if it be taken regularly.

Summary. Respiratory measurements were made on a group of 75 medical students and on 13 football players in active training. As a result of these measurements the following conclusions were drawn:

1. "Heavy" smoking (20 or more cigarettes a day) for several years does not significantly diminish the respiratory efficiency in the performance of mild and moderately severe exercise.
2. Athletic individuals are not much more efficient than sedentary persons in the performance of mild exertion, but are considerably more efficient in carrying out moderately severe exercise.
3. Individuals who have once been highly trained, remain extremely efficient in their breathing for a number of years after giving up active training, provided they take fairly regular exercise.

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REVIEWS.

A RADIOLOGICAL STUDY OF THE PARANASAL SINUSES AND MASTOIDS. By AMÉDÉE GRANGER, K.C.B., K.C.I., M.D., F.A.C.R., Professor of Radiology, Louisiana State University Medical Center, and Director of the Department of Radiology, Louisiana State Charity Hospital, New Orleans. Pp. 186; 113 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$5.50.

THE otolaryngologist who is not satisfied with his knowledge of sinus films will do well to read the text of this book and study the plates presented. By so doing his information concerning the correct interpretation of sinus roentgenograms will be greatly increased. In addition he will learn if his roentgenologist is securing the detail which Granger demonstrates. This is especially true of the sphenoid air spaces concerning which Roentgen ray information is not infrequently unsatisfactory. The plates of illustrative cases demonstrate the author's points very clearly. In lesser degree the same may be said of the mastoid presentation. Unfortunately the illustrative mastoid films do not always give the detail called for in the author's text.

K. H.

CLINICAL ROENTGEN PATHOLOGY OF THORACIC LESIONS. By WILLIAM H. MEYER, M.D., Professor of Roentgenology in the New York Post-Graduate Medical School of Columbia University, etc. Pp. 272; 183 engravings. Philadelphia: Lea & Febiger, 1932. Price, \$6.00.

THE author has presented in a very concise and unique manner a book on diseases of the thorax and its contents. I presume that this book was prepared particularly for matriculates of his school. It contains detailed systematic plans for the examination of the chest, and anyone who follows such a plan would be prevented from overlooking most lesions. The author has considered technique, pathology and most of the adjuncts that radiologists use in determining the nature of the lesion which they are studying.

The discussion of the diseases with their roentgenographic manifestations is very concise. In fact, one obtains the impression that it is too concise in some instances; but at least it does give the student the usual textbook appearance of certain conditions, and if he is interested he will look elsewhere for additional data. The book contains no bibliography but the Reviewer gains the impres-

sion that the author has searched rather widely for his material, and this combined with his own large experience makes the book worth while.

The illustrations are very good, especially when one considers that they are all negatives. The pencil drawings greatly aid in the interpretation of the lesions. Unfortunately, the illustrations are not uniform. Namely, the heart is at times on one side, and then on the other. This makes it difficult to interpret when the legend and the side on the illustration do not correspond. The print is readable and the subjects are set apart throughout the entire book. The paper is glossy, which makes it a little more difficult to read.

E. P.

NERVOUS INDIGESTION. By WALTER C. ALVAREZ, M.D. Pp. 297. New York: Paul B. Hoeber, Inc., 1930. Price, \$3.75.

In this volume the scientist or intelligent physician will find little of interest. From the standpoint of sound, physiological data on the question of nervous influences on the gastrointestinal tract this book offers nothing that cannot be found in much greater detail, and in far more satisfactory manner in "The Mechanics of the Digestive Tract" by the same author. Even the sketchy material offered on this question loses considerably in value because of the lack of an adequate bibliography. It is true that the author tells many interesting anecdotes about people with nervous disorders of the digestive tract. Yet, even in this regard, it would be a safe venture that the average practitioner from coast to coast could ably swap stories about neurotics with Dr. Alvarez for hours without feeling in the least a sense of inferiority. It is the avowed purpose of the book to focus the attention of students of medicine, and of general practitioners, on the importance of functional disorders of the digestive tract. The degree to which this is accomplished must be judged by each individual reader.

M. F.

THE DIAGNOSIS AND TREATMENT OF VENEREAL DISEASES IN GENERAL PRACTICE. By L. W. HARRISON, D.S.O., M.B., CH.B., F.R.C.P.E., Brevet Colonel, R.A.M.C., and K.H.P. (RET.). Director of Venereal Department, St. Thomas's Hospital. With a chapter on The Medico-Legal Aspects, etc., by F. G. CROOKSHANK, M.D., F.R.C.P., etc. Pp. 567; 79 illustrations. Fourth edition. New York: Oxford University Press, 1931.

THIS book, the fourth, enlarged edition of a well-known text, presents the views of one of the best known and highly organized

venereal disease services in the world, that of Great Britain, and is an exceptionally concise and trustworthy manual for the general practitioner. Condensation of material adds to its practical value as a small but authoritative volume in which the author shows an extraordinary acquaintance with the literature of his subject.

The regional presentation of material and the attempt to interweave the manifestations of syphilis and gonorrhea, while of some service to the practitioner, probably makes less appeal to the specialist in urology or syphilology as such.

The frankness of the chapter dealing with the prevention of venereal diseases is a welcome relief from the usual prudery that envelops these issues.

J. S.

NOSOKOMEION, QUARTERLY HOSPITAL REVIEW. First special number, containing the reports presented to the Vienna Congress. Pp. 492. Stuttgart: V. W. Kohlhammer, 1931. Price, 15 marks.

THE first special issue of *Nosokomeion*, a quarterly hospital review, published by V. W. Kohlhammer, Stuttgart, presents the reports of the second International Hospital Congress held in Vienna, June 8 to 14, 1931. This volume consisting of 492 pages is printed in German, French and English, although French is the official language of the Congress. The advantage to the hospital world generally of this triple language presentation is evident since the vast majority at least of administrators of American hospitals are not sufficiently acquainted with German and French to enable them to secure the greatest benefit from a volume not so printed.

Few realized in 1927 the far-reaching effect of a preliminary meeting held in the Red Cross Headquarters in Paris, France, at which 14 countries were represented. The writer of this review, being present on this occasion, noted the very marked interest displayed in the formation of an International Hospital Congress by those present. The first meeting of this Congress in Atlantic City in 1929 brought forth some splendid contributions to the hospital literature and attracted the attendance of the representatives of over two score countries. The Vienna Congress, at which delegates from almost every government of size in the world were in attendance, apparently exceeded in size and literary contribution the Atlantic City meeting.

The program consisted of the discussion of 10 major subjects, including construction, nursing, medical services, physiotherapy, occupational therapy and social service. A splendid address was delivered by Prof. Dr. Julius Tandler, Director of Vienna Public Health and Social Welfare Services, who is the president of the organizing committee, opened the Congress.

Dr. René Sand, of the Red Cross Society, who acted as the official

host in the name of the Red Cross to the organizing committee, and who served most effectively as interpreter, reviews in this volume the development of the International Hospital movement.

One of the outstanding contributions was that included in a report of the Committee on Nursing, headed by Miss Christine Reimann, chairman of this committee, and a representative of the the International Nursing Association on the Ratio of Nurses to Patients. This committee exhaustibly discusses the nursing situation throughout 22 countries. One is struck with the great variance in patients per nurse, in working hours, in annual vacation and in working conditions under which nurses labor throughout the world. There still exist in many countries relics of the pre-Nightingale era in regard to requiring too long tours of duty and of exacting from nurses, drudgery which appears both unfair to the nurses and economically expensive to the hospital. More than that, this committee demonstrates that where too long working hours are found and where the labors of the nurse are physically too exacting, the average number of days lost yearly for sickness rises rapidly. Thus it amounts from 4.1 for the trained nurse and 5.9 for the student nurse in the United States, to 16.8 and 14.9 respectively in Austria. In scanning the report of the conditions under which nurses work throughout the world, one cannot help but conclude that the nursing situation here in the United States ranks rather high, notwithstanding the unfavorable comment which one hears so frequently.

A splendid discussion by Dr. Wirth, of Frankfurt, urges on The Unification of Hospital Nomenclature. This matter should interest not only governmental and private statistical agencies, but all hospitals throughout the world. The classification of diseases and causes of death certainly requires some attempt at standardization.

What Dr. Alter, of Düsseldorf, has termed "the third indispensable service" of the hospital, *i. e.*, the care of the soul through occupational therapy, social service and other humanitarian activities, is discussed by Dr. Wortman, of Hilversum, Netherlands. Professor von Noorden, of Vienna, presents in this volume a splendid article on "Nutritional Service in the Hospital." Dr. Alter, of Düsseldorf, discusses the place of neurology and psychiatry in the general hospital. Dr. Layton, of London, presents a report outlining the advantages which public health derives from the coöperation of social insurance in the hospital. Dr. Corwin, of New York, presents the problem of the development and integration of dispensaries in and with the hospital.

Not only to hospital administrators is this number of *Nosokomeion* of great interest, but it contains much useful information which should appeal to physicians, sociologists and all others interested in community health.

J. D.

CLINICAL DIETETICS. By HARRY GAUSS, M.S., M.D., F.A.C.P., Instructor in Medicine, University of Colorado, School of Medicine, Assisted by E. V. GAUSS, B.A., formerly Assistant Dietitian, Presbyterian Hospital, Denver, Colo. Pp. 490; 59 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$8.00.

THE outgrowth of a course of lectures on the subject given by the senior author in the medical school of the University of Colorado, the book is a clear, concise, orderly presentation of the subject. Lacking the great detail of the usual more extensive works on dietetics, it nevertheless gives the practical essentials. This fact, together with the numerous specimen diets worked out on a weekly program basis, should make it very useful to practitioners. There are few criticisms: pernicious anemia is attributed to a simple avitaminosis, an unwarranted assumption. There is no mention of the possible use of high protein diets in nephrosis. It is fallacious to assume that a patient who has been put on the 5 elimination diets noted and has not been made free of symptoms is not troubled with food allergy—it merely proves that he is sensitive to more than a single food. Finally, there is no bread but whole wheat in the authors' opinion, but then every dietitian rides a hobby.

R. K.

COSMIC CONSCIOUSNESS. By RICHARD MAURICE BUCKE, M.D., Formerly Medical Superintendent of the Asylum for the Insane, London, Canada. Pp. 384; 1 illustration. New York: E. P. Dutton & Co., Inc., 1931. Price, \$5.00.

By "Cosmic Consciousness" the author signifies a form higher than either the self-consciousness possessed by the ordinary man or the simple consciousness of animals. Concerned with the life and order of the whole universe, this form of intellectual enlightenment is looked upon as a state of moral exaltation which has been experienced by a relatively few individuals, but in increasing numbers as civilization progresses. The major part of the book describes 14 instances of "Cosmic Consciousness," from Gautama the Buddha to Edward Carpenter, with 36 lesser or doubtful instances.

The bibliographic history of this book is unusual. Passing through 3 small editions between 1901 and 1912, it was practically lost for 10 years, after which Dutton has published 4 editions in the past eight. To the Reviewer the book proved but mildly interesting and still less enlightening, with a tiresome mysticism and frequent unjustifiable deductions. Nevertheless William James considered it "an addition to psychology of first rate importance" and the cover carries equally favorable comments. Let each reader decide for himself.

E. K.

A HISTORY OF SCIENCE. By WILLIAM CECIL DAMPIER DAMPIER-WHETHAM, M.A., F.R.S., Fellow and sometime Senior Tutor of Trinity College, Cambridge; Fellow of Winchester College. Pp. 514; 14 figures. New York: The Macmillan Company, 1931. Price, \$4.00.

ALTHOUGH it has been rather generally accepted that the scientists, artists and artisans of modern times have done far more to benefit the human race than have rulers, statesmen and warriors, still it is the history of the latter group that is best known and most carefully studied. Only in the past two decades has an increasing interest in the History of Science been apparent, as manifested by the growing list of recent books on the subject, by the Journal "Isis," by works like Sarton's splendid first volumes of an Introduction to the History of Science and by the various national and international societies interested in the subject.

The demand within a year for another edition of this thoughtful book by Dampier-Whetham is another encouraging example of recent trends and shows the interest created by such works in the minds of a wider circle than those of professional scientists. And such popularity has in no sense been obtained by sacrifices to a popular style. Scholarly but readable, it accomplishes in 10 chapters an account of science from the dawn of civilization down to its most recent developments. The "New Era in Physics," for instance, devotes 63 pages to radio-activity, quantum mechanics, relativity and the other surprising developments of the past 40 years. Nor are philosophic applications shirked; in the last chapter especially, "Scientific Philosophy and Its Outlook," mathematics, logic and metaphysics are frankly applied to such concepts as determinism and religion with the resultant confessions of ignorance now so popular among physicists. "But, now or later, intelligible mechanism will fail, and we shall be left face to face with the awful mystery which is reality." "*Credo quia impossibile*," said Tertullian. E. K.

FIGHTING DISEASE WITH DRUGS. Edited by JOHN C. KRANTZ, JR., with an introduction by Dr. JAMES H. BEAL. A publication of The National Conference of Pharmaceutical Research. Pp. 230; 27 illustrations. Baltimore: Williams & Wilkins Company, 1931. Price, \$2.00.

THIS is a symposium containing 12 chapters, each written by a specialist, dealing with the history of pharmacy, the sources, chemistry, and standardization of drugs and the relation of modern pharmacy to the community and to science in general. It is written for the average layman, for the purpose of acquainting him with the

part played by pharmacists and pharmacy in the development of modern therapeutics. Such a reader will be left with a higher opinion of the practitioner of pharmacy than he had before, and with a good idea of the problems which have been solved and which await solution in the development of chemical and biologic remedies. For the physician, the chapters on Dawn of Pharmacy (Dohme), Bacteria-made Drugs and Vitamins (Anderson) and Drugs Made by Man (Adams and Kamm) contain much of interest.

C. S.

BOOKS RECEIVED.

NEW BOOKS.

The Practice of Contraception. Edited by MARGARET SANGER and HANNAH M. STONE, M.D. With a Foreword by ROBERT L. DICKINSON, M.D. Pp. 316; 22 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$4.00.

Neoplasms of Domesticated Animals. (Mayo Clinic Monograph.) By WILLIAM H. FELDMAN, D.V.M., M.S., Division of Experimental Surgery and Pathology, The Mayo Foundation. With a Foreword by CHARLES H. MAYO, M.D. Pp. 410; 193 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$6.00.

Gynecological Roentgenology. By JULIUS JARCHO, M.D., F.A.C.S., Attending Gynecologist and Obstetrician, Sydenham Hospital, New York. Vol. 13 of *Annals of Roentgenology*. Edited by JAMES T. CASE, M.D., Professor of Roentgenology, Northwestern University Medical College, Chicago. Pp. 571; 273 illustrations, 5 colored plates. New York: Paul B. Hoeber, Inc., 1931. Price, \$20.00.

Experimental Researches on Precancerous Changes in the Skin and Skin Cancer. By GUSTAV GULDBERG. Pp. 223; 26 illustrations. Copenhagen: Levin & Munksgaard, 1931.

The Harvey Lectures, 1930-31, Series 26: Pp. 186; illustrated. Baltimore: The Williams & Wilkins Company, 1931. Price, \$4.00.

Acta Societatis Medicorum Fennicae. Edited by S. E. WICHMANN, Professor Ord. Universitatis. "Duodecim," Series B., Vol. XV. Pp. 546; illustrated. "Duodecim" Series B, Vol. XVI. Pp. 695; illustrated with charts and tables. Helsinki, 1931.

The White House Conference Publications on Child Health and Protection. New York: The Century Company, 1932. I. *Health Protection for the Preschool Child.* By GEORGE TRUMAN PALMER, DR. P. H., Chairman, Subcommittee on Statistics, MAHEW DERRYBERRY, Research Assistant and PHILIP VAN INGEN, M.D., Chairman, Committee on Medical Care for Children. Pp. 275; 50 charts and numerous tables. (1931.) Price, \$2.50. II. *Body Mechanics: Education and Practice.* Report of the Subcommittee on Orthopedics and Body Mechanics, ROBERT B. OSGOOD, M.D., Chairman. Pp. 166; illustrated. Price, \$1.50. III. *Psychology and Psychiatry in Pediatrics: The Problem.* Report of the Subcommittee on Psychology and Psychiatry, BRONSON CROTHERS, M.D., Chairman. Pp. 146. Price, \$1.50.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Histologic Studies of the Bone Marrow in Fasted and Polyneuritic Pigeons.—Of increasing interest is the attention that is being paid to anemias which develop as a result of certain nutritional deficiencies. MOORE and BARLOW (*J. Exper. Med.*, 1931, 54, 761) have investigated the bone marrow in pigeons fed upon a diet of rice contrasted with a group which were fasted. The conclusions drawn by the authors are to the effect that the changes in the bone marrow in the fasted and rice-diseased pigeons are essentially the same. In pure vitamin B deficiency there is degeneration and edema and slight endothelial proliferation of the small vascular channels but with active hematopoiesis. The anemia of rice disease in pigeons is apparently not particularly related to vitamin B deficiency but depends upon the starvation anemia.

Reticulocyte Response to Glutamic Acid in Pernicious Anemia.—The use of glutamic acid as an antianemic substance was suggested to LICHTMAN (*Proc. Soc. Exper. Biol. and Med.*, 1931, 29, 153) by the fact that the acid may be condensed into pyrrolidonecarboxylic acid, which is one of the isolated substances in the liver tissue identified by West, Howe and Dakin as pyrrole precursors active in Addisonian anemia. Furthermore, several other authors have found the acid and certain other amino acids are effective in the treatment of the anemia of rats who are fed on an exclusive milk diet. These particular pyrrole substances, it is suggested, are probably liberated from certain protein foods through the action of normal gastric digestion and are then decomposed so that their products after absorption are capable of playing a part in the synthesis of hemoglobin and erythrocyte stroma. In pernicious anemia the necessary substances are not available to the organisms due to some deficiency of the gastrointestinal tract. Lichtman therefore fed glutamic acid to 4 patients with pernicious anemia. A condiment, Suzuki, exceedingly popular in Japan which contains

sodium-glutamate was the form in which the glutamic acid was administered. He found that there was some slight reticulocyte response in the 4 patients studied, the maximum response being 6 per cent. There was no rise in the hemoglobin or erythrocyte count except in 1 patient in which the hemoglobin went up but the red cells were not increased. The conclusion is drawn that sodium glutamate, while not completely devoid of activity as shown by definite reticulocyte response in the 4 cases studied, is not however an effective substitute for liver extract in the treatment of pernicious anemia.

SURGERY

UNDER THE CHARGE OF
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The Peptic Genesis of Gastric and Duodenal Ulcer.—LUDAN and WOLFF (*Surg., Gynec. and Obst.*, 1931, 53, 621) say that a survey of the experiences acquired will show that, in the biochemical theory, there is an exceedingly good explanation of the nature as well as the location of the peptic lesions with ulcer formation, confined to the esophagus, cardia, area of the pyloric glands, duodenum, jejunum (postoperatively) and in Meckel's diverticulum. Everywhere the lesion is to be found in the area of activity of the hydrochloric acid. The presence of free hydrochloric acid has likewise proved to be a regular finding. This biochemical theory now advanced anew and further developed by Buechner has, in fact, been taken up and confirmed by several leading investigators. Aschoff and Kolk also in recent monographs have expressed the opinion that the gastric juice has again marched to the foreground as a genetic factor of ulcer, contending however, that the excess of hydrochloric acid is due to a "Dysharmonie des Vegetativen Nervensystems." The main object would be to control and reduce as far as possible, the production of hydrochloric acid by suitable dieting in accordance with the experience gained chiefly through the Pavlov school. Considering surgical therapy with its rather varying measures, the operation, Billroth I, which reduces the production of hydrochloric acid, removes that part of the gastral system which is most susceptible to ulceration, while retaining to the greatest possible extent the normal topography and normal discharging conditions, is probably the method that yields the best results and shows extremely few or no cases of relapse or postoperative ulcer.

The Roentgen-rays and Radium in the Diagnosis and Treatment of Carcinoma of the Bladder.—PFAHLER (*Surg., Gynec. and Obst.*, 1931, 53, 680) says that pneumocystography is a valuable means of determining the presence, size, outline, position and amount of infiltration of a carcinoma of the bladder. It can be carried out by any careful roentgenologist with sterile catheter, atomizer, bulb and a hemostatic forceps. Radiotherapy involves treatment by radium in the form of capsules, needles or seeds (glass or gold) and by the use of deep roentgenotherapy,

either alone or before or after electrocoagulation. It seems that electrocoagulation is better than excision, followed by radium or Roentgen ray treatment. Some very encouraging results have been obtained by irradiation alone. Under such treatment the patient is usually relieved of hemorrhage and pain. If results can be made permanent and percentage of cures increased, and if in the early stages the growth can be destroyed cystoscopically, it will be a great step in advance.

Paget's Disease—A Predisposing Factor to Osteogenic Sarcoma.—COLEY and SHARP (*Arch. Surg.*, 1931, 23, 918) state that it was found from a study of cases of osteogenic sarcoma in Memorial Hospital, that in no patient was this condition associated with Paget's disease prior to the age of 50 years. In a collected series from Memorial Hospital and the Bone Registry of 71 cases of osteogenic sarcoma in patients over 50 years of age, Paget's disease was found to be a predisposing factor to osteogenic sarcoma in 28 per cent. Men are affected five times more frequently than women—among patients with the two diseases associated. In general it may be said that osteogenic sarcoma in patients over 50 has the same sites of predilection as in younger persons. A patient over 50 with osteogenic sarcoma of the skull presumably has Paget's disease. When osteogenic sarcoma is associated with Paget's disease it invariably develops in a bone showing the characteristic changes of Paget's disease rather than in an otherwise normal bone. Evidence is presented to show that Paget's disease is present from 10 to 15 years or more prior to the development of a complicating osteogenic sarcoma. The duration of life is shortened by the association of osteogenic sarcoma with Paget's disease, as determined by a comparative study of a group of patients of the same age without osteogenic sarcoma. No record has been found of the survival for 5 years of a patient with osteogenic sarcoma and Paget's disease under any method of treatment. Paget's sarcoma has proved to be relatively resistant to radiation.

Some Thoughts on the Problem of Cancer Control.—COLEY (*Am. J. Surg.*, 1931, 14, 605) says that a considerable portion of the funds raised for cancer control should be expended in the field of collecting more facts especially more accurate first-hand information, as to the geographic distribution of cancer and especially data that may account for the wide variation in incidence. Little advance may be expected in the surgical treatment of cancer, but in the field of Roentgen ray and radium with increasing knowledge of the action of these agents and with improved technique, considerable advance may be anticipated. Radiation has already displaced surgery in certain fields, *i. e.*, cancer of the skin, of the cervix and oral cancer. It is rapidly becoming recognized that most cases of cancer can best be treated by a combination of surgery and radiation, rather than by the use of either alone. A systematic attempt should be made to give the undergraduate medical student much better clinical instruction in the early diagnosis of cancer than he has had in the past and even more important is it to provide numerous centers where intensive postgraduate instruction may be obtained. The results of study by the various organizations and individuals working on the problem of cancer, including both the clinical and laboratory aspects, should be given wide publicity.

THERAPEUTICS

UNDER THE CHARGE OF
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The Treatment of Angina Pectoris With Tissue Extract.—Following suggestive leads given by the observations of Frey and Kraut, Gley and Kisthinios, Schwartzman and others, WOLFFE, FINDLAY and DESSEN (*Ann. Inter. Med.*, 1931, 5, 625) prepared a purified extract of pancreas according to the method of Gley and Kisthinios. They find this extract to be entirely free of histamin and virtually free of insulin. They report experiments upon animals and observations on the therapeutic effects in man. Administration of the extract to animals produces a sharp drop in blood pressure followed by fairly prolonged maintenance of the pressure at a lowered level. It also antagonizes more or less effectively the vasoconstrictor action of epinephrin. In addition it slows the heart rate. The extract does not seem to be antigenic nor does it have demonstrable toxic effects upon animals. The extract was standardized upon rabbits, one hypotensive unit being that amount which produces a just appreciable fall in blood pressure when injected intravenously into a rabbit weighing 2 kg. For clinical trial a concentrated extract was employed which contained 15 units per cc. The extract was given intramuscularly to a series of patients suffering from angina pectoris which was unrelieved or insignificantly influenced by the usual methods of treatment. The doses employed varied from 60 to 150 units, the usual dose being 75 units. No significant ill effects were observed in this group of patients and complete clinical relief of pain was secured in 55 per cent, partial relief in 30 per cent while in 15 per cent there was no benefit. One patient was relieved both of his angina and of a severe associated intermittent claudication. The authors present this early report with the belief that the extract promises to be of great value as a therapeutic agent and in the hope that it may promptly be put to sufficient controlled clinical trial to determine its value and limitations. They point out that the extract is not a hormone but that its action depends upon a vasodilator principle which is either adenylic acid or adnosine, both of which may be obtained from various body tissues.

Intravenous Quinidin Therapy.—PADILLA and COSSIO (*Arch. des Mal. du Cœur, etc.*, 1931, 24, 401) made careful trials to determine whether or not the intravenous administration of quinidin could be carried out safely in man and found that such was the case provided that certain conditions were met. The solution should not be more concentrated than 5 per cent of quinidin in physiologic saline. The

injection should be carried out slowly. The patient should be recumbent during the injection. The single dose of quinidin should be about 0.5 gm. for the majority of cases and even in exceptional cases it should not exceed a maximum of 0.15 gm. of the sulphate for each 10 kilos of the patient's body weight. Following these established conditions, the authors administered quinidin sulphate intravenously to a series of patients without once encountering serious toxic effects. Reporting 4 cases in some detail and analyzing the previous literature they conclude that the intravenous injection of the drug is especially indicated in patients with prolonged paroxysmal tachycardia, especially where it has proved resistant to the more usual methods of treatment. Such injections of quinidin are almost invariably effective in immediately arresting the tachycardia and restoring normal rhythm. The intravenous injection of quinidin is also indicated in certain cases of auricular flutter, especially in paroxysmal types. In these conditions, however, its chief action is to diminish the ventricular rate by depressing auriculo-ventricular conduction. Minor toxic symptoms may appear such as occasional marked pain along the course of the injected vein which seems to depend chiefly upon a too rapid injection. With the rapid return of normal rhythm and much slower rate in cases of paroxysmal tachycardia transitory symptoms of lassitude, pallor, cold sweating and slight visual disturbances are occasionally seen. There are also occasional instances in which the patient complains of rather intense precordial oppression which may or may not be accompanied by dyspnea, profound lassitude, ringing in the ears, vertigo, nausea, vomiting, etc. These symptoms, however, are rarely either lasting or important.

The Reaction to Nitrites in Angina and Hypertension.—It is a well established fact that nitrites are capable of relieving the pain in the majority of patients with the anginal syndrome, whether this pain be associated with hypertension or not. It is further a well known fact that the nitrites generally produce a rapid but transitory fall in blood pressure. There has been considerable speculation as to the mechanism by which the nitrites accomplish the relief of anginal pain, and especially as to the relationship between this specific relief of pain and their vasodilator effects. In order to throw further light upon these problems, BURGESS (*Ann. Int. Med.*, 1931, 5, 441) carried on a group of carefully controlled clinical investigations from which he concludes as follows: Neither nitroglycerin nor amyl nitrite produce any consistent blood pressure change other than slight transitory lowering in normal persons or in persons with simple or complicated hypertension. Although a brief reduction of pressure follows their administration in the majority of cases with angina, close study shows that the relief of pain is independent of this effect, both in point of time and in point of the extent of the lowering of pressure. It is a demonstrated fact, however, that the nitrites cause a pronounced increase in coronary blood flow which also is apparently unrelated to their action upon the systemic circulation. The author concludes from these observations that the pain of angina is probably due to a relative ischemia of the myocardium and that its relief by nitrites is due to their rapid production of increased flow through the coronaries with improved nutrition of the heart muscle.

PEDIATRICS

UNDER THE CHARGE OF

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Phosphorus Metabolism in Infants.—WITT (*Am. J. Dis. Child.*, 1932, 43, 306) studied the phosphorus metabolism in a group of 5 apparently healthy infants, each of whom was fed breast milk and cow's milk mixtures during alternate periods. This was done to exclude variations that might arise as a result of constitutional differences in the experimental subjects. Individual 24 specimens have no value for metabolic investigations. Analysis of the average values for three consecutive 24-hour periods shows distinct differences produced by change of diet. The average intake of phosphorus with cow's milk was 0.654 gm. per 24 hours and with breast milk 0.258 gm. The total output during the periods when cow's milk was used was almost four times as great as that during the periods of breast feeding. There was an output of 0.394 gm. per 24 hours during cow's milk feedings as compared to 0.108 gm. during the periods of breast milk feeding. The increased output during the feeding of cow's milk is due to a great extent to the increased phosphorus during these periods. The average excretion of phosphorus in the urine was 0.275 gm. per 24 hours during the period of cow's milk feeding and 0.064 gm. when breast milk was fed. The average value for phosphorus excreted in the feces was 0.119 gm. per 24 hours for cow's milk and 0.044 gm. for breast milk. The actual phosphorus absorbed by the infants studied was considerably more during the periods of cow's milk feeding; the average value for cow's milk, 0.535 gm. per 24 hours, compared to 0.213 gm. for breast milk. The average percentage absorption for breast milk was 83.1 per cent as compared to 81.1 per cent for cow's milk. The actual amounts of phosphorus retained were considerably greater during the periods when cow's milk was used, possibly as the result of a greater intake, and for this reason it was difficult to compare the percentage values for retentions. Over 50 per cent of the phosphorus intake was retained by each infant during the periods when it was breast fed, and the values ranged from 51 to 63.8 per cent, with an average of 58.1 per cent. During the periods when cow's milk feedings were given the retention was always below 50 per cent, the maximum being 44.2 per cent and the minimum 29.2 per cent. The values per kilogram obtained during the periods when the baby was breast fed indicated that the optimal absorption and retention of the phosphorus in breast milk occurred in the earliest months of life.

Basal Metabolism of Normal Children—The Puberty Reaction.—POPPER and MULIER (*Am. J. Dis. Child.*, 1932, 43, 327) studied the basal metabolism of 28 girls and 10 boys from 10 to 16 years of age at intervals of 6 months to a year above a period of from 1 to 4 years. It was found that there was an increase in the basal metabolic rate in the prepubescent period, reaching its maximum around the time when catamenia was established in girls, and sexual maturity in boys, with a

subsequent decline afterward. There was no uniformity in the height of the increased metabolism or in the duration of the increase. Some of these children had no other symptoms of an enlarged thyroid gland. Others presented such symptoms as enlarged thyroid gland, tremor, nervousness, vasomotor instability, cardiac murmur and tachycardia. All of these symptoms disappeared as the basal metabolic rate returned to the previous normal level, when puberty was well established. The authors feel that an increased basal metabolism is physiologic during pubescence. This increased metabolism coincides with the physiologic age rather than with the chronologic age, and occurs earlier in girls than in boys, coincident with their earlier pubescence. As there seems to be an individual variation in the height and duration of the increased metabolism, it makes the adoption of normal standards difficult for this important age period. The increased basal metabolism may be associated with symptoms simulating organic heart disease or more especially exophthalmic goiter. In evaluating high metabolic figures at this period, the clinical manifestations of pubescence have to be considered. Exophthalmic goiter is rare before puberty and should not be confused with the physiologic overactivity of the thyroid gland in pubescence, which is temporary and the prognosis of which is excellent.

The Seasonal Incidence of Some of the Diseases of Childhood.—HERRMAN (*Arch. Ped.*, 1932, 49, 73) states that human beings are subject to the same biologic laws as plants and animals. The physical, physiologic and chemical conditions differ at different seasons of the year. The time of greatest susceptibility to many diseases is in the late winter and spring. As several functional neuroses and constitutional conditions, as well as infectious diseases, present this seasonal variation, it seems likely that an increased virulence of infectious material is the primary etiologic factor. The injurious effect seems to depend on a sudden transition or an abrupt change in some meteorologic element. Apparently there are certain persons who are unable to adjust themselves quickly to these changes. Although it is impossible at the present time to be certain what the exciting agent is, it is most likely some form of radiation. Such a hypothesis is supported by the fact that some of the functional neuroses are much more common in some years than in others. Experimental work on laboratory animals would seem to offer the most promising field for a solution of the problem. In such experimentation the various factors involved could be separated, modified and controlled and the effect of different forms of radiation of different wave lengths determined and artificial climates produced. As the vast majority of persons cannot move to a different climate, and as one cannot control to any great extent the air one breathes and the radiation to which one is exposed, efforts must be directed largely to increasing the resistance of the person. This can be done mainly in three ways: The first is by preventing the birth of the defective and the unfit, thus raising the average resistance of the community. The second is by active immunization of infants against the infectious diseases. The third is by providing infants, children and pregnant mothers with a diet containing an adequate amount of vitamins, and by exposing them out-of-doors in the winter and spring so that they may increase their ability to adjust themselves to sudden changes in climate.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Macular Atrophy of the Skin.—CHARGIN and SILVER (*Arch. Derm. and Syph.*, 1931, 24, 614) review the literature of this rare but interesting dermatologic condition and definitely clarify the issue, proposing the following simple but satisfactory classification:

- A. Primary (not preceded by known dermatoses).
 - 1. Anetoderma Jadassohn.
 - 2. Anetoderma Schweninger and Buzzi.
- B. Secondary (preceded by known dermatoses).
 - 1. Syphilis (atrophia maculosa syphilitica).
 - 2. Tuberculosis and lupus erythematoses.
 - 3. Leprosy.
 - 4. Other dermatoses.
- C. Mixed types of atrophy (macular atrophy and acrodermatitis chronica atrophicans).

The Anetoderma erythematosum of Jadassohn varies greatly in onset and course but for the most part consists of erythematous macular lesions that may pale in the center to form a ring or even become confluent and terminate in atrophic areas with at times a central baglike protrusion which on pressure seems to herniate into the skin. The lesions occur mostly over the trunk and limbs and are found three times more frequently in females than in males. The Schweninger and Buzzi type originally described under the term "multiple benign tumor-like new growths of the skin" differs mostly in the absence of preceding inflammatory changes. Syphilis is by far the commonest cause of secondary macular atrophy. The process may simply be associated with syphilis or, more commonly, replace a previous syphilitic eruption, usually of the papular type. The condition usually appears during the second or third year of a syphilitic infection but much longer time intervals are on record. No entirely satisfactory etiology has been established for the entire group, although the endocrine theory of Singer seems the most plausible. Pathologically the essential changes are fragmentation, contraction and finally disappearance of the elastic tissue.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Fistula Formation in Cervical Cancer.—In 254 cases of carcinoma of the cervix treated by radium in Cardiff Royal Infirmary, fistulae have appeared in 22 cases (8.7 per cent) according to STRACHAN (*J. Obst. and Gynec. Brit. Empire*, 1931, 38, 542). Of the 22 cases, fistula formation occurred only within the last 2 months of life in 8 cases, so that, unless a practically complete follow-up is kept and unless this complication is specifically inquired into, a certain proportion of fistula cases will fail to be included in statistics. In the majority of cases nothing can be done for the fistulae forming in the course of cervical cancer. Especially is this the case in vesicovaginal fistula and in any fistula when growing carcinomatous tissue occupies its edges. In some few cases in which clinical cure appears to have taken place and when active carcinoma is not present, extreme fibrosis and puckering makes the success of a closure operation problematical at least. Although cure of the fistula is unlikely much may be done in the course of radiation to prevent this complication. Prior to radiation the bowel should be thoroughly emptied and at the completion of irradiation a self-retaining catheter should be inserted and retained during the time that the radium is in position. In this way the bladder and bowel can be kept at a distance from the focus of the gamma rays and out of harm's way. Appropriate packing off of the vaginal walls by gauze soaked in flavine or other antiseptic is also employed. If a flat vaginal applicator is employed, the long diameter of the box should be placed transversely in the pelvis and never anteroposteriorly. In this way not only is excessive anterior or posterior radiation avoided but the lateral fornices and bases of the broad ligaments receive the maximum radiation. Similarly when needles are employed they should not be carried too far toward the anterior or posterior fornices.

Ovarian Neoplasms.—At the Eighth British Congress of Obstetrics and Gynecology which was held at Glasgow in April, 1931, there was presented a very interesting and complete symposium upon the subject of ovarian neoplasms. The contribution which BLAIR BELL (*J. Obst. and Gynec. Brit. Emp.*, 1931, 38, 249) made to this meeting was concerned with the pathology and clinical features of these tumors. He stated that the relation of age, parity and other points in the histories of the patients and the frequency of unilateral and bilateral neoplasms are worthy of note but they show little difference between innocent and malignant neoplasms. The difficulty in diagnosis arises most commonly in respect to bilateral tumors of a solid or papillary nature,

especially as free fluid is often associated with both the innocent and the malignant. The points to consider are: the presence or absence of a primary malignant growth, masses in the liver, occurrence of adhesions, age and general condition of the patient. Ascites depends on whether the tumor is sufficiently free and out of the pelvis to irritate the peritoneum or whether there are implantations in the general peritoneal cavity. The only treatment considered is surgical. Innocent tumors require removal but an effort should always be made to conserve some normal ovarian tissue. In malignant ovarian disease he is of the opinion that Roentgen rays and radium do more harm than good while chemotherapy with lead may help but it is usually combined with surgery. If the tumor rises above the pelvic brim, laparotomy is advised but attention is drawn to the advantage of the vaginal route for removing cysts in the true pelvis during pregnancy. Long incisions are favored for the larger cystadenomata in people of middle age, owing to the possibility of malignant disease and adhesions, which are more easily separated if the cyst is untapped. He states that it is essential to remove the uterine fundus and both adnexa in all doubtful cases even if localized to one side.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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The Eye Symptoms of Brain Tumors.—According to STÄHLI (*Schweizer. med. Wchnschr.*, 1931, 61, 702) subjective and objective eye changes are of frequent occurrence and of great diagnostic importance in patients with tumors of the brain. Choked disks are found in about 80 per cent of cerebral tumors and in about 90 per cent of cerebellar and cerebello-pontine angle tumors. Patients with choked disks may complain of transient obscurations of vision, but central vision usually remains good, often for months. It fails earlier in cerebellar than in cerebral tumors. Choked disks are less frequent in metastatic than in primary tumors of the brain. In tumors of the hypophysis, simple descending optic atrophy is more frequent than choked disks. Homonymous hemianopsia occurs in about one-fifth of all cerebral tumors. In almost half the cases it is caused by a lesion involving the occipital lobe. In the rest, some other part of the optic tract is affected. Quadrant hemianopsias are seen less frequently in brain tumors than in softenings following thromboses or hemorrhages. Bitemporal hemianopsia is the result of a lesion involving the optic chiasm and is the classical symptom of tumor of the hypophysis. Binasal hemianopsia is seldom found since a bilateral lesion in the region of the chiasm would be necessary for its production.

Nystagmus is seen much more frequently in tumors of the cerebellum, of the cerebello-pontine angle, and of the fourth ventricle than in those of the cerebrum. Paralysis of the sixth nerve is more frequent in brain tumors than paralysis of the third. Supranuclear lesions of the nerves to the eye muscles are characterized by conjugate paralysis or conjugate deviations. Lateral conjugate paralysis is most common in tumor of the pons. Vertical conjugate paralysis is characteristic of lesions of the corpora quadrigemina and the pineal body. Consideration of the neighborhood signs is often necessary to determine whether the involvement of the third or sixth nerve is at the base of the brain or in the nuclear region. Pupillary changes are not of much value in the diagnosis of brain tumors with the possible exception of lesions in the peduncles or corpora quadrigemina. The fifth nerve is involved most frequently in tumors of the pons and cerebello-pontine angle. Usually the motor portion is not affected. Neuroparalytic keratitis is sometimes associated in tumors of the pons, but rarely in angle tumors. Exophthalmos is seen in about 8 per cent of tumors of the anterior and middle fossa and usually means invasion of the orbit. Occasionally an isolated metastasis in the orbit has been found to be the cause of the exophthalmos. Aphasia and alexia are focal symptoms of a circumscribed lesion of the cerebral cortex, usually on the left side and most often in the occipital lobe.

In tumors of the cerebrum, choked disk occurs in about 80 per cent, simple optic atrophy in about 1 per cent. Vision usually remains good for a long time. Choked disk is most likely to be absent in tumors of the motor region of the cortex, of the convexity of the hemisphere, of the corpus callosum, and of the base, especially metastatic tumors. Tumors arising from the meninges are less apt to cause choked disks than are tumors in the brain substance. Hemianopsia is seen in about one-fifth of the cases and is usually homonymous. In one-half of the cases with homonymous hemianopsia, the tumor is situated in the occipital lobe and in these, visual hallucinations, aphasia or alexia are apt to be associated. Homonymous hemianopsia may also be caused through injury to the optic tract by tumors at the base, in the internal capsule, or in the basal ganglia. Eye muscle disturbances occur in about one-third of the cases, and usually mean a basal lesion. The third nerve is more frequently involved than the sixth. Conjugate paralysis and nystagmus are rare. Isolated fourth nerve paralysis is very rare and usually points to a lesion of the corpora quadrigemina or the pineal region. Involvement of the fifth nerve is rare and is confined essentially to tumors of the base. Exophthalmos is rare.

In cerebellar tumors, choked disks occur in about 90 per cent of the cases and reduction of vision takes place earlier and is of higher degree than in cerebral tumors. Hemianopsia, aphasia and visual hallucinations are not seen except occasionally as secondary pressure effects. Nystagmus and ocular muscle disturbances are much more common than in cerebral tumors. Usually the sixth nerve is involved, more rarely the third; occasionally there is conjugate paralysis or conjugate deviation. The fifth nerve is somewhat more frequently involved than in cerebral tumors. Loss of corneal reflex is frequently an early symptom. Neuroparalytic keratitis is infrequent and exophthalmos is practically never seen.

In tumors of the hypophysis, simple optic atrophy, bitemporal hemianopsia and third nerve paralysis are the characteristic findings. Choked disks occur in about 20 per cent of the cases without acromegaly and less frequently in the cases with acromegaly. Simple optic atrophy is about twice as frequent as choked disk. Bitemporal hemianopsia is found in more than 50 per cent of the cases. Paralysis of the third nerve occurs in about one-fifth of the cases without acromegaly and in one-tenth of the cases with acromegaly. Nystagmus and conjugate paralysis do not occur. Some of the cases with acromegaly show thickening and lengthening of the lids, occasionally with edema, papillomatous formation, or abnormal pigmentation and exophthalmos.

Tumors of the pons are most frequently solitary tubercles, gliomas, or gliosarcomas and are seen often in young people. Choked disks are found in only about one-third of the cases and often not until the late stages. Sixth nerve paralysis occurs in about four-fifths of the cases, is often bilateral, and often accompanied by facial paralysis on the same side. In about one-half the cases, crossed hemiplegia is present. The most characteristic symptom is lateral conjugate paralysis, sometimes bilateral, which occurs in about one-third of the cases, especially when accompanied by crossed hemiparesis, or a complete homolateral facial paralysis. The third nerve is less frequently involved. When present, along with crossed hemiparesis (Weber's syndrome), the tumor has involved the peduncle or the third nerve nucleus. Complete facial paralysis occurs in about one-half the cases—most frequently it is associated with crossed hemiparesis (Millard-Gubler syndrome). Involvement of the fifth nerve is frequent but never isolated. When accompanied by facial paralysis, neuroparalytic keratitis is apt to occur. Nystagmus is not seen.

In tumors of the fourth ventricle, choked disks and nystagmus are more frequent than in tumors of the pons. In acoustic tumors, choked disks are seldom absent. Nystagmus occurs in about one-third of the cases usually with associated cerebellar signs such as ataxia and vertigo. The facial nerve is involved in about one-half the cases. Fifth and sixth nerve paralysis occurs in about one-fourth of the cases. In tumors of the peduncle, often tuberculous, choked disks are rare. Most characteristic is third nerve paralysis with contralateral hemiplegia (Weber's syndrome) or contralateral tremor (Benedikt's syndrome). Tumors in the tegmentum cause oculomotor paralysis with crossed hemianesthesia, and tumors in the fillet, oculomotor paralysis with crossed ataxia.

Tumors of the corpora quadrigemina and pineal region are characterized by paralysis of elevation and depression of the eyes, vertical conjugate paralysis, which is present in about one-fifth of the cases. The third nerve is sometimes involved, sometimes bilaterally; less frequently the fourth or sixth. In about one-fourth of the cases the facial nerve is affected, usually only in its lower branches. Nystagmus is not infrequent. Choked disks occur in about three-fourths of the cases. Involvement of the acoustic nerve is often an important sign.

Christian's Syndrome.—The syndrome characterized by exophthalmos, diabetes insipidus and defects in membranous bones (Christian's syndrome) has been described in about 25 cases under various names,

viz., xanthomatosis, lipemic diabetes, Niemann-Pick's disease and Gaucher's disease. The clinical features of the syndrome are as variable as the histologic picture which has been described under such names as sarcoma, myeloid-sarcoma, myeloid-endothelioma, myxoxanthoma, granuloma, giant cell tumor and giant cell sarcoma. JASON and ABRAHAM (*Am. J. Ophthalmol.*, 1931, 14, 1146) have observed the course of the disease in a child aged 3 years and 3 months, normal at birth and of healthy stock, who had proptosis of the right eye for at least 19 months; who had lesions of the bones of the skull, shown by Roentgen ray, for at least 14 months, had loose teeth and gingivitis, urine negative, blood cholesterol at the upper limit of normal. The lesion improved under radium treatment.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Regarding Morphological and Functional Changes of the Internal Ear in Arteriosclerosis.—Based on a study of microscopic sections, functional records of hearing, clinical data and autopsy protocols, FABINYI (*Laryngoscope*, 1931, 41, 663) reported the findings in 26 cases of clinically diagnosed arteriosclerosis—all of which were confirmed at autopsy. Nineteen were males. The ages ranged from 47 to 78 years; 15 were over 60 years of age. In addition to changes in the large vessels elsewhere, the majority showed sclerotic changes in the internal carotid and cerebral arteries. Recognizing arteriosclerosis and "presbycusis" as normal human involutionary circumstance, the author found that in most instances of marked arteriosclerosis the loss of hearing was greater than in persons with moderate arteriosclerosis; and was usually accompanied by more or less atrophy of the spiral ganglion, the nerve fibers in the osseous spinal lamina and the organ of Corti in the basal coil. In the small bloodvessels of the meatus and modiolus the changes consisted of proliferation of intima and subendothelial tissue, hypertrophy of internal elastic lamina and medial thickening.

Local Lesions in Diphtheria and Their Significance in the Generalized Infection.—Excepting *B. tetani*, no microorganism pathogenic for man can do so much harm by elaborating a soluble toxin from its local point of attack than *B. diphtheriæ*. So much so that the Klebs-Loeffler bacillus has come to be regarded virtually as noninvasive or at most only of a feeble local invasiveness; and that the real damage to the human organism results from the systemic dissemination of its powerful exotoxin. Even so, the local pathologico-anatomic features, and to a degree the intensity of the generalized manifestations, of clinical diphtheria can be influenced by several other well-known factors; not the least of which is environment.

For instance, as KIRCH (*Ztschr. f. Laryngol., Rhinol.*, 1931, 20, 81)

points out that the pseudomembranous lesion caused by *B. diphtheriæ* is usually less deep and adherent on ciliated columnar epithelium (nasal, laryngotracheal) than on the more commonly involved stratified squamous epithelium of the oropharynx. In other words, less bacillary invasion occurs on ciliated epithelium. From his observations, the author goes on to state that: (1) diphtheria bacilli do not multiply as freely in the blood stream as streptococci or staphylococci; (2) that they disappear from the blood when the local pseudomembrane begins to separate; and (3) Klebs-Loeffler bacilli were found not infrequently in myocardium, kidney, spleen and liver of fatal cases; but not in the nervous tissue. He admits, however, that in many instances no *B. diphtheriæ* were encountered in degenerated heart muscle.

Abstractor's Comment. Excepting in the overwhelming infections of the agonal period, it is difficult to establish that bacteria actually multiply in the blood stream—even so notoriously invasive forms as anthrax, pneumococci, streptococci, etc. Experimentally, it is well-known that the blood tends to rid itself promptly and thoroughly of enormous doses of pathogenic microbes. All the characteristic cardiac lesions of fatal human diphtheria can be reproduced in the experimental animal by injecting bacteria-free diphtheria toxin.

RADIOLOGY

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Chemical Effects of Roentgen Rays.—A large number of dyes were exposed by CLARK and FITCH (*Radiol.*, 1931, 17, 285) to Roentgen rays under the same conditions of irradiation, to determine, if possible, some of the general types of structures giving good visible color changes. Some of those showing the most promise from the point of view of stability and degree of color change were the triphenyl methane, alizarin, thiazin and indigo types. The magnitude of the field is such that in all probability the color most suitable as an intensity indicator has not yet been found.

Unrecognized Vertebral Fracture versus Kummell's Disease.—The diagnosis of Kummell's disease, or traumatic spondylitis, is being made by roentgenologists with increasing frequency, to the consternation of insurers and industrial accidents boards, often on the unsupported evidence of a solitary wedge-shaped vertebra. The author states that the cause is always trauma, either by direct force against the spine or the impaction of a heavy object on the shoulders and neck. Severe pain in the affected portion of the spine follows but gradually disappears. After a somewhat longer time severe pains recur and motor and sensory

symptoms appear. Still later a definite kyphos and gibbus results. In the opinion of O'BRIEN (*Radiol.*, 1931, 17, 661) what Kummell has described is unrecognized, hence untreated, fracture of the spine, and presents roentgenograms of illustrative cases.

Traumatic Arthritis.—The most important physiotherapeutic measure for traumatic arthritis is rest, according to KEY (*Arch. Phys. Therap., X-ray, Rad.*, 1931, 17, 550). Complete rest may be effected by plaster casts, but it must not be continued indefinitely. Partial rest, obtained by supports of elastic, leather or metal, or by protection from strain, such as may be accomplished by altering the shoes or correcting the posture, is often of benefit. Heat, massage and manipulation are popular. Heat and massage relieve pain temporarily and are grateful to the patient, but there is no evidence that they are otherwise beneficial. Manipulation is dangerous, and if used injudiciously may keep a joint sore for many months and result in permanent harm.

The Diagnosis and Treatment of Intestinal Tuberculosis.—For the diagnosis of intestinal tuberculosis, WATSON and CALLANDER (*Arch. Phys. Therap., X-ray, Rad.*, 1931, 17, 532) consider the roentgenologic examination as most important, and they follow the technique of Brown and Sampson, but often employ the opaque enema in addition to the ingested meal. In the treatment they emphasize the importance of absolute rest in bed. The diet is modified, and the "smooth diet" of Alvarez is often prescribed. Cod-liver oil is given after each meal in a dose of 1 tablespoonful in 3 ounces of tomato juice, served cold, or in orange juice. Solar radiation and the ultraviolet lamp are employed interchangeably. The lamp is used cautiously and a dose of 30 minutes each to back and front at a distance of 30 inches is never exceeded.

Diathermy of the Rectum and Pelvic Colon.—SOPER (*Arch. Phys. Therap., X-ray, Rad.*, 1931, 17, 545) regards diathermy as the treatment of choice for precancerous polyps, early cancer that projects into the bowel, and simple and tuberculous ulcers of the rectum and pelvic colon. In late inoperable cancer the visible growth can be destroyed and bleeding checked by this means. Adenocarcinoma is by far the most common growth encountered in the rectum and pelvis. The author has destroyed eight such growths in the past 3 years by diathermy without recurrence. Simple ulcers heal quickly. Tuberculous ulcer involving the anal canal responds well to the bipolar method.

Yeast Infection of the Lungs.—Yeast mold infection is rare and usually attacks the skin, according to HEALY and MORRISON (*Am. J. Roentgenol. and Rad. Therap.*, 1931, 26, 408), but it sometimes gains entrance into the body and produces tubercles, tissue destruction and abscess formation in the lungs, spleen or kidney, and occasionally attacks the meninges and brain. The disease affects all ages, but is found most often after middle life. Blastomycosis is practically confined to Illinois and is found in and about Chicago. Coccidioidal granuloma occurs principally in California and this is also true of torulosis. In mild cases of yeast infection of the lungs the general condition of the patient is good; the sputum is mucopurulent, often scanty, and contains no blood;

physical examination is negative or reveals only a few râles; the condition may last for weeks or months and go on to spontaneous cure or turn into the severe type. The severe type closely resembles phthisis. The patient becomes emaciated, has a hectic fever, and the expectoration is often hemorrhagic. At times the sputum has a yeasty odor. The roentgenologic picture is similar to that of tuberculosis. The diagnosis is based on the absence of tubercle bacilli and the presence of yeast cells in the sputum. It is essential that the sputum be collected in sterile receptacles after the patient has gargled with warm sterile water, and the specimen must be examined immediately. The authors have observed 5 cases. In the first case, their attention was attracted by the disparity between the appearance of the patient and the extent of the lesion shown by the roentgenograms. From the roentgenogram he should have been very ill, but he was only a little below par. *Saccharomyces busse* was found in the sputum. The 4 other cases clinically followed a course similar to tuberculosis, and this was the tentative roentgenologic opinion in several. The yeast fungi found in all cases were of the *Blastomycetes imperfecti* class, of the genus *Oidium*.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Inheritance of Mental Characteristics.—EAST (*Mental Hygiene*, 1931, 15, 45) states that normal mentality and feeble-mindedness are a pair of contrasting unit characters inherited as if the difference between them were due to a single unit of heredity, a single gene. Thus the basis upon which the geneticist constructs his concept of the inheritance of mental attributes is obvious. Inheritance in man has been found to be the same as in any other sexually reproducing organism. And there is plenty of evidence to show that mental traits are transmitted in precisely the same manner as other traits. The normal variability in general intelligence and in special aptitudes, which is shown in every population group, is intelligible only on the assumption that a limited number of genes have varied into what one may call the plus and minus types. It is impossible to determine the number of such mutations because genes are not unite in their action; one particular gene may have 100 times as much influence in altering intelligence as some other particular gene. Yet it is unnecessary to postulate mutations in any great number of genes to account for the variability in human mentality that is actually observed. From 20 to 40 mutations would be ample. Twenty plus and 20 minus genes affecting mentality would give the opportunity for over 1 million gene patterns in the germ cells. Theoretically, it would be possible for any one of these genes to mutate to a

type that would produce a breakdown in the mental machinery. Under such conditions normal mentality and defective mentality would behave as so-called unit characters in crosses; that is to say, they would behave as if the difference followed the distribution of a single gene. And the defective mentality could exist in numerous grades, due to action of the other genes that go to make the physical basis of the mind; just as normal mentality can exist in numerous grades for similar reasons.

Contribution to the Differential Diagnosis of Epileptic Disorders.—

BAUM (*München. med. Wchnschr.*, 1931, 78, 25) presents a patient in whom the symptoms had been regarded for years as due to an idiopathic epilepsy, despite the late age of onset of attacks. The mildness of the original head injury and the symptomless interval of 2 years allowed the traumatic basis to be overlooked. The patient was a man, aged 38 years, who, while serving during the World War in the Landwehr, was admitted to a hospital in November, 1914, on account of head wounds from a hand grenade. Minor injuries of the right cheek and lower jaw were present and the patient was discharged by Christmas. He returned to the line where he remained perfectly well until July, 1917, when he suffered from an epileptic fit. He remained under medical observation at various hospitals during the next 8 months and was finally discharged from the army in March, 1918, with a pension of $33\frac{1}{3}$ per cent. Epileptic attacks of a mild character continued, at intervals varying from $1\frac{1}{2}$ to 4 weeks, being more frequent when he worked hard. As he had injured himself on many occasions, he found difficulty in obtaining employment and in August, 1930, he sought an increase in the amount of his pension. He was accordingly admitted to a hospital, where no neurologic abnormality was detected. His mentality was characterized by dullness, slowness of cerebration, inattention and irritability. One or two insignificant scars were apparent over the cheek and right side of the head. A Roentgen ray revealed a large number of small, irregular metallic splinters embedded in the soft tissues of the right side of the face and in the right hemisphere. A number lay in the region of the scalp wound, and two larger fragments were visible in the depths of the right parietooccipital lobes.

A Pathologic Contribution to the Concept of Neurosomatic Deterioration in Epilepsy, With Record of Two Cases.—HODSKINS and YAKOVLEV (*Am. J. of Psychiat.*, 1931, 10, 663) present 2 cases which clinically, seem quite different; however, both show the same essential features: epilepsy and the symptomatologic pattern of neurosomatic deterioration. In the first case, that of a child, deterioration developed more rapidly and was more destructive, in 9 years leading to the ultimate stage of neurosomatic deterioration, viz., profound dementia and cerebral flexion paraplegia. In the second case, that of a man aged 66 years, with late epilepsy, the neurologic picture characteristic of neurosomatic deterioration developed more slowly, was not so dramatic, and the symptomatologic pattern was one that could be identified with arteriosclerotic Parkinsonism. Pathologically, in both cases was found evidence of a primary vascular cerebral lesion, which was, in the first case, an acute lesion, viz., meningioencephalitis; in the second case, a chronic lesion, viz., cerebral arteriosclerosis. In both the primary pathologic

lesion was the starting point of the same chronic degenerative process affecting principally the frontal cortex (third layer and basal ganglic pallidum and peduncular hypothalamic formation). This last chronic degenerative and atrophic secondary process seems to be the most plausible cause of the clinical symptoms of neurosomatic deterioration. The predominant localization of this process in the third layer of the cortex and the globus pallidus appears to agree with the fundamental features of the clinical syndrome which was manifested by disturbances in the psychomotor sphere, viz., dementia and progressive rigidity.

Epilepsy as an Exaggerated Form of Normal Cerebral Inhibition.—ROSETT (*Am. J. of Psychiat.*, 1931, 10, 673) states that the phenomena of the seizure, whatever the indirect underlying cause may be, are directly caused by that process of interference of nerve impulses, with the result of their mutual extinction, which is known as inhibition. Such inhibition is in itself a normal process, to which the phenomena of thought, imagery and dreams owe their existence. Even under normal conditions there is a wide range in the degree of facility with which cerebral inhibition takes place, thus making for the fact that some persons can exert their powers of attention with greater intensity than can other persons. Any condition that will disturb the chemical, physical or mechanical balance of the nervous system, may result in a acilitation of the normal process of cerebral inhibition, with the appearance of epileptic seizures as a result.

PATHOLOGY AND BACTERIOLOGY

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Tumors of the Suprarenal Gland With Special Reference to Carcinoma of the Cortex: Report of a Case.—MEYER and FRUMMES (*Arch. Int. Med.*, 1931, 48, 611) have presented a case of a girl, aged 13 years, who suffered from a malignant tumor of the suprarenal cortex, and who exhibited some of the characteristic symptoms of the genito-suprarenal syndrome seen with tumors of the suprarenal cortex with neoplastic tendencies. The case report is followed by a review and discussion of the subject with special reference to the diagnostic symptoms composing this syndrome, and the prognosis and the treatment of such cases. Another section of the paper deals with the pathology of tumors of the suprarenal gland.

Tumors of the Heart and Pericardium: Pathology, Symptomatology and Report of 9 Cases.—YATER (*Arch. Int. Med.*, 1931, 48, 627) presents a comprehensive review of the subject of primary and secondary tumors of the heart and pericardium; and points out that these tumors

are rare and the majority are without symptoms and are therefore of interest only to the pathologist. He discusses the symptomatology under these two headings: clinical types not suggestive of tumor of the heart; and clinical types suggestive of tumor of heart. Over 150 cases of primary tumors of the heart have been reported in the literature and about 20 per cent of these were malignant. "Primary tumors of the heart are myxoma, fibroma, sarcoma, rhabdomyoma and less commonly lipoma, endothelioma and a few rare forms. Varices occur in the heart, and nodular leukemic infiltrations are occasionally seen." Primary tumors of the pericardium are usually sarcoma or lipoma. Secondary tumors of the heart show a great variation in type, size and distribution; the lesions are usually carcinomatous or sarcomatous. The primary growth may occur in any organ. The author gives a detailed report of 9 cases of tumor of the heart and mentions 2 additional cases of later observation.

On the Susceptibility of the Gopher (*Citellus Tridecemlineatus*) to *Mycobacterium Tuberculosis*.—FELDMAN (*Am. J. Path.*, 1931, 7, 139) reports that with the use of original strains of the *Mycobacterium tuberculosis* derived from human bovine and avian sources, using either the subcutaneous, intraperitoneal or intravenous routes of injection, he succeeded in infecting the striped gopher with each of the three bacillary forms. The animals died at intervals of from 36 to 78 days; or were sacrificed from 40 to 91 days after inoculation. Definite lesions of tuberculosis were observed as a consequence of each of the three forms of the tubercle bacillus. The animal appears to be more susceptible to the human and bovine types of the tubercle bacillus than to those derived from avian sources. The degree and extent of infection varied with the route of inoculation, being most pronounced in the animals inoculated intravenously. The histopathology of the lesions produced by the three types of tubercle bacillus in this animal is essentially of the same character. It is interesting that this animal is, to some degree at least, susceptible by the ordinary routes of injection to the avian strain.

Silicosis and the Effect of Silica on the Growth of the Tubercle Bacillus.—The well-known fact that patients with silicosis practically always succumb to pulmonary tuberculosis makes particularly interesting the cultural results of PRICE (*Proc. Exper. Biol. and Med.*, 1931, 28, 819) who reports that the addition of 1 cc. of sodium silicate or silicic acid, standardized to contain 1 mg. silica, to every 100 cc. of modified Dorset's egg medium enhances the growth and development of the tubercle bacillus in the test tube. This is apparent by a lessening of the latent period and a greater luxuriance of growth. The stimulating effect of these silicon compounds is continuous throughout the whole period of growth. These observations cover 20 initial cultures of the tubercle bacillus, isolated indirectly through guinea-pig inoculation or directly from human sources as urine, sputum, pus, cerebrospinal fluid, and in one instance ascitic fluid. Colonies have been observed in 6 to 9 days; growth continues rapidly, and in some instances can be considered luxuriant in 3 weeks, or even less.

Idiopathic Fevers and Agglutination Tests With *Brucella Abortus* Antigen.—From a study of a large number (3716) of blood serums made in the various Public Health Laboratories of the State of New York. BAYNE-JONES (*Am. J. Pub. Health*, 1930, 20, 1313) in a search for unsuspected cases of undulant fever found that 64 (1.72 per cent) gave agglutination with *Brucella abortus* antigen in a dilution of 1 in 100 which was considered diagnostic. In 10 cases of typhoid fever the serum gave agglutination reactions using this same antigen in dilutions of 1 in 10 to 1 in 40—not diagnostic. On the other hand 180 specimens from patients suspected of having typhoid fever were entirely negative. The result of this study seemed to indicate a fairly high degree of specificity for the reaction. Farming and occupations associated with farming and cattle raising were those most frequently correlated with positive reactions for undulant fever in this series. It is suggested that valuable information will be obtained if this test is done routinely on the serum of patients suffering from obscure and periodical fevers, arthritis, abdominal and intestinal disorders as well as of cases suspected of having typhoid fever or tuberculosis. The widespread occurrence of the disease in New York State would suggest that this disease should be thought of in all febrile conditions.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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A Bacteriologic Study of "Colds" on an Isolated Tropical-Island (St. John, United States Virgin Islands, West Indies).—MILAM and SMILLIE (*J. Exper. Med.*, 1931, 53, 733) report investigations which form a part of a study of colds in isolated communities under different environmental conditions. Previous studies have been made in Alabama and Labrador, and this third group was conducted in St. John, one of the Virgin Islands. Two arresting facts were noted in the last studies: (1) The mild type of colds that were encountered; (2) the constancy and uniformity of the bacteriologic flora of the nasopharynx. If the previous studies in Labrador and Alabama are considered in conjunction with the St. John studies, it is noted that certain flora of the nasopharynx are found consistently in uniform numbers in all areas. The results suggest that colds are incited by some specific agent with which we are not as yet familiar. They suggest also that the secondary and more severe symptoms associated with colds may be due to certain aerobic flora commonly found in the nasopharynx. Types of pneumococci which are virulent (to white mice) and true Pfeiffer's bacilli requiring both V and X substance (and forming indol?)

seem to be of particular importance in these secondary infections. The studies indicate that the specific agent which initiates colds is infectious in nature, and spread by direct contact, with an incubation period of 1 to 3 days. There is strong evidence that environmental factors, particularly reduction in atmospheric temperature, have some influence upon the incidence of colds. The investigations indicate that colds are less common and much less severe in the tropics than in the temperate zone. The basic nasopharyngeal flora in normal persons in St. John is similar to that of normal persons in Labrador and Alabama. Pfeiffer's bacilli are much less common in St. John than in the temperate zone. Hemolytic staphylococci are prevalent in the tropics, hemolytic streptococci are rare. Pneumococci are prevalent in St. John but are avirulent. Fixed Types I, II and III are rare. The basic nasopharyngeal flora in St. John was quite constant throughout all seasons and in all groups of people. No change occurred in the nasopharyngeal flora in a group of persons who developed colds. The seasonal incidence curve of acute colds in St. John was a replica in miniature of the same curve for the United States. No colds occurred during the very warm period from June to October. An epidemic of colds in December was coincident with a slight but abrupt drop in atmospheric temperature.

Points to be Considered in Case of a Poliomyelitis Epidemic.—LEAKE (*U. S. Pub. Health Rep.*, 1929, 44, 1819) considers 3 weeks a suitable period of quarantine, especially since the patient needs rest for that period. He regards healthy, acute, rather than chronic carriers as the most usual means of spread. Diminishing human contacts in general is advocated, but the closing of places of assembly is not advocated under ordinary conditions. Organization for treatment of preparalytic cases by convalescent serum is important, but it is pointed out that the method is still on trial. With respect to after treatment the following is said: Probably the greatest good that the State Department of Health can do is in the prevention of deformities and crippling as an aftermath of recognized paralytic cases. The early treatment should certainly be under the control of the local physician. In connection with the circularization and publicity, to aid in the early diagnosis, emphasis should be placed on the necessity of absolute and prolonged rest in bed, in a position to forestall and prevent any tendency to deformity, by fixation if necessary. There comes a time in practically every case, however, and it may come very soon, when the proper care becomes too irksome for the family to carry on without the moral support and stimulus of some such agency as a consultant orthopedist with nurses or physiotherapists particularly skilled and trained in this disease; and it is a rare family which can afford the expense of such prolonged, continuous and special skill unless the treatment is supervised under some such auspices as those of the state or municipal department of health. Adequate hospitalization of these cases is out of the question.

The Pyrogenic Reaction to Concentrated Antipneumococcus Serums, with Respect to Certain Serum Constituents.—FELTON and KAUFFMANN (*J. Exp. Med.*, 1931, 49, 337) studied the nature of the protein with which antibody of the pneumococcus obtained from immune horse serum is associated to find, if possible, any differences that may exist

between preparations that are satisfactory on intravenous injection and those that produce chills or other untoward reactions. From the results of the investigations with preparations made by three different methods, the authors draw the following conclusions: (1) Chill-producing lots still contain some material precipitable at a pH value of from 4.8 to 5.2 in a neutral salt concentration which is about one-twentieth normal, whereas under these conditions good preparations contain but little. (2) Chill-producing lots have a slightly higher phosphorus and perhaps a higher lipoid content than good ones; the differences are so slight, however, as to indicate that the residuum of these agents in the final preparations may not be responsible for pyrogenic action. Unsatisfactory preparations contain more ammonia and nonprotein nitrogen than do those that are suitable for intravenous injection.

The Movements of Epidemic Meningitis,—1915–1930.—HEDRICH (*U. S. Pub. Health Rep.*, 1931, 46, 2709) reviews some of the general epidemiologic characteristics of epidemic meningitis, and the recent movements of the disease as to time and place. The available evidence indicates that during epidemics surprisingly large proportions of the population may at one time or another become infected with the meningococcus. Under highly congested conditions, as in army camps, it appears that practically the entire population may become infected once or oftener during epidemics. Probably far less than 1 per cent of such infections result in clinical attack, as annual attack rates in excess of 1 per 1000 population are rare. The case fatality, however, is heavy; approximately one-half of the reported cases died during the recent epidemic, in spite of fairly widespread use of serum. Meningitis became increasingly prevalent in Europe shortly after the opening of the World War, and in the United States shortly after her entry, when mobilization began. The highest attack rates in England came in 1915 and in the United States in 1918. In 1928–1930 the disease was again epidemic in most parts of the world. The interval between the last two epidemic maxima was 11 years in the United States and a few years longer in most European countries. The interepidemic interval is highly variable. It has oftenest been 6 to 12 years, but some areas have run as long as 25 years without epidemics. Massachusetts, for example, has had no appreciable epidemic since about 1905, and New York City only a minor one, namely, in 1928–1930. Over broad areas, such as large groups of states, epidemics have appeared, not as sporadic explosions but as crests of rather smooth and systematic waves, the rising and declining phases of which have covered a period of 3 to 6 years or longer. Within smaller areas, such as individual cities, the movements of the disease have been less systematic. Neither of the last two epidemics was synchronous in different parts of the United States, some regions having lagged 2 years behind others. The time rate of epidemic development within specific areas and the rate of geographic movement are very much slower for meningitis than for influenza. In the 1918 epidemic the reported attack rates were highest in the southern sections, probably due to the large number of military concentration camps; the Rocky Mountain States had the lowest rates. In the 1928 outbreak the Southern States had the lowest and the Mountain States the highest rates.

Typhus Fever: The Rat Flea, *Xenopsylla Cheopis*, in Experimental Transmission.—DYER and his associates (*U. S. Pub. Health Rep.*, 1931, 46, 1869) claims that on epidemiologic grounds there is an association between typhus fever and the handling of foodstuffs and rats. In the present experimental work the tropical rat flea was shown to be able to convey typhus infection from one white rat to another.

Three Outbreaks of Food Poisoning Apparently Due to *Bacillus Enteritidis*, *Bacillus Paratyphosus B* (Aertrycke Type) and *Bacillus Paratyphosus A*, Respectively.—GEIGER and his associates (*U. S. Pub. Health Rep.*, 1931, 46, 1565) found the incubation period in each of the outbreaks to be 2 to 4 hours, which, together with the relatively short duration of symptoms, indicate preformed toxins rather than infections. In the outbreak due to *B. enteritidis* the source was considered as most likely to be incompletely cooked veal. In the case of *B. paratyphosus B* infections the source was considered to be rice pudding and this was probably infected by a commercial rat virus. In the outbreak due to *B. paratyphosus A* a human carrier was the most probable source and an egg-shouffle-shrimp mixture was the means of transmission from the carrier to the victims.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 14, 1932

Heterochronism in the Single Fiber Nerve Muscle Complex.—H. GRUNDFEST (from the Eldridge Johnson Foundation for Medical Physics, University of Pennsylvania). The question of isochronism between muscle and nerve has been studied in the single fiber nerve muscle complex of the retrolingual membrane. The single fiber preparation has several advantages over the gross preparation. The measurements obtained are, first of all, free from the statistical averaging which occurs when a large number of fibers are used. Also, on direct stimulation only the muscle fiber stimulated responds while the entire motor unit responds to indirect stimulation through the nerve. It is, therefore, possible to distinguish very clearly between the two types of stimulation.

The results obtained indicate that the law of isochronism is not valid for the retrolingual preparation. Furthermore, Lapique's theory regarding curarization does not apply to this preparation, since curari does not affect the chronaxie of muscle fibers. These results are in accordance with the work of Lucas and of Rushton. This agreement is strengthened by the fact that compound curves of the type described by these observers can be obtained from the retrolingual preparation. In this case, as already pointed out, it can be demonstrated directly that a break in the strength duration curve is accompanied by a change to a new excitable element. The suppressed portions of the two components of the compound curve are also obtainable.

Data have also been obtained which cast doubt upon the value of chronaxie as a concept. The chronaxie is found to vary with size of electrode and with structural modification of the excitable tissue. It is, therefore, impossible to speak of a definite experimentally measurable chronaxie and unwise to apply the chronaxie concept to theoretical speculation.

The Effect of Different Salts on the Swelling of Lipoids.—M. SPIEGEL-ADOLF (from the D. J. McCarthy Foundation for Neurological Research, Temple University). With reference to the important rôle that the abnormal swelling of the brain plays in nervous diseases, the following experiments were made with the purpose of enabling *in vitro* studies of the effects of therapeutics on lipoids. According to the method of Keeser, the lecithin sols were made out of egg lecithin of Merck. The viscosity of such solutions was studied by the method of Ostwald. In conformity with the results of Handovsky and Wagner, the depressing effect of neutral salts on lecithin sols could be demonstrated. But, while those authors missed any influence of hypnotics on the viscosity, it could be shown that the latter was much more lowered by the addition of bromid than by any other neutral salt, including thiocyanate and the salt mixtures used by Pierre Marie in the treatment of epilepsy. The results became only more distinct when protein was added to the mixture of lecithin sol and salt. Different proteins seemed to behave in a different way. The greatest effect could be observed in pseudoglobulin. The marked effect of bromid on the viscosity of lecithin sols could not be explained by the law of Hofmeister, according to which iodine and thiocyanate ions should be more efficient. But it could be observed that KI containing some free iodine had a greater influence on the viscosity than the pure salt. So it was suggested that the effect of the bromid salt was due to the action of the oxydized bromine, perhaps on the group of unsaturated fatty acid in the lecithin molecule. In fact, measurements of the refraction of lecithin and lecithin salt mixtures by the interferometer of Zeiss seem to agree fairly well with this hypothesis. It could be demonstrated that, while the refraction of a lecithin KCl mixture was almost exactly equal to the sum of the interferometric values of the single components, addition of KBr and of KI, especially when the latter contained free iodine, seemed to increase the interferometric value of lecithin. These results, which are in conformity with those obtained by the viscosity measurements, point to the close relations between chemical and colloid chemical properties in colloids. Preliminary investigations have further shown that a reaction of drugs used as hypnotics with lecithin could be detected by changes of the refraction, while they were missed in a case in which a poison inducing convulsions was added to the lecithin sol.

The Central Mechanism of Tonic Spasms, Rigor and Catalepsy, Produced by Toxins.—E. SPIEGEL (from the D. J. McCarthy Foundation for Neurological Research, Temple University). The tonic spasms following extirpation of the parathyroids are observed even after a transverse section of the brain stem behind the nucleus ruber and

after extirpation of the cerebellum (Spiegel and Nishikawa). The spinal cord, medulla oblongata and pons are sufficient for the genesis of such spasms.

The rigor observed in narcosis is only partly due to paralysis of the cortex. After one-sided injuries of the motor area, the frontal, or the temporal lobe, this rigor is more marked in the extensor muscles of the opposite side (Spiegel and Bernis, Spiegel and Hotta). A bilateral action of the toxin upon subcortical apparatus is here combined with the one-sided increase of the excitability of such mechanisms, due to the one-sided cortical injuries. The development of the local rigor in tetanus poisoning depends upon impulses from higher centers to the spinal cord. This rigor is less marked on the side of a hemisection of the spinal cord; in animals (rats and cats) whose corpus striatum had been extirpated a form of flexor rigidity develops instead of the extensor rigidity, whereas the destruction of the cortex has no such influence. (Spiegel and Bruwer.)

On the other hand, the increase of tonicity produced by bulbo-capnin is influenced by cortical impulses. The injection of this poison in cats whose motor area had been destroyed on one side produces asymmetries of the posture of the limbs and a torticollis-like posture of the head, which are missed after the operation on the cortex alone. (Spiegel and Krisch.)

The diminution of voluntary movements in the so-called bulbo-capnin catalepsy is not due to paralysis of the cortex, as the excitability of the motor area is not lowered by such doses of bulbocapnin as are sufficient to produce the catalepsy. This fact, and the observation that larger doses of bulbocapnin produce symptoms of central, especially cortical stimulation (Schaltenbrand, De Jong), lead to the assumption that the bulbocapnin catalepsy is due to a central inhibition, as a consequence of weak stimulation of the forebrain. As small doses of poisons acting mainly upon the cortex (like small doses of cocain) produce, at the most, only very slight cataleptiform reactions, one might assume that the catalepsy in bulbocapnin poisoning is due to the action of this poison, not only upon the cortex, but also upon subcortical ganglia of the forebrain. One can break through the central inhibition in bulbocapnin catalepsy by the inhalation of $\text{CO}_2\text{-O}_2$ mixtures (Spiegel and Kaufman), or by the injection of larger doses of cocain (Spiegel and Evrard), thus producing an effect of these poisons similar to that observed in stuporous patients.

The Study of the Heart Action With the Roentgen Cinematograph.—W. EDWARD CHAMBERLAIN (from the Laboratory of Radiology, Temple University). The Roentgen cinematograph, as designed and built by Dr. H. E. Ruggles, of the University of California, is a device which enables us to obtain serial instantaneous teleroentgenograms of the beating human heart at the rate of exactly 15 per second. Such serial teleroentgenograms have been photographed onto motion picture film, and the resulting cinematographic demonstration is of great interest to the cardiac physiologist.

Using Dr. Ruggles' device, we obtained serial roentgenograms of normal cases and cases with mitral stenosis and mitral regurgitation.

By means of careful measurements upon such serial films we have plotted the movements of various parts of the cardiac silhouette upon a time scale. The resulting curves, which have become known as skiacardiograms, are of great interest from the standpoint of the physiology and pathology of valvular disease, and a comparison of our findings with postmortem studies has suggested that the method is capable of being put to clinical use.

This presentation consists of a demonstration of the motion picture of the normal beating heart, followed by a lantern slide demonstration of the method of exposing and measuring the films, and a series of typical skiacardiograms of normal and diseased hearts. Skiacardiographic curves bear a closer resemblance to myographic tracings of heart muscle than to volume curves obtained with the plethysmograph.

The simplicity and economy of the "slit method" of "Roentgen kymography" recommend that procedure for the study of movements of the borders of the heart shadow, but there are technical difficulties in the way of accurately locating the observed points upon the cardiac silhouette. The chief advantages of our method lie in our ability to definitely identify the part of the cardiac silhouette whose motion we are studying and to obtain simultaneous graphs of the movements of all parts of the silhouette for the same heart cycle.

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Correction

In the paper entitled "Iodin in Exophthalmic Goiter," by Jacob Lerman, M.D., and James H. Means, M.D. (this *Journal*, 1931, 181, 750), the second paragraph should read as follows: "The average basal metabolism just after admission to the hospital was +57. After a resting period varying from 2 to 9 days the average basal metabolism was +53. After treatment with ethyl iodid it was +24. The average daily fall in metabolism was 3.7 points, varying from 1.8 to 7.4."

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ORIGINAL ARTICLES.

THE CARDIAC MANIFESTATIONS OF HYPERTHYROIDISM.

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THE cardiac manifestations of hyperthyroidism, palpitation, tachycardia and hyperactivity—the “overdemonstrativeness” of Cabot¹—are among the earliest and most constant phenomena of the disease, while occasionally arrhythmias of various types and even myocardial insufficiency and congestive heart failure are encountered. Among the many theories that have been advanced to explain these phenomena almost all have assumed the heart to be specifically affected, and as a result the various terms “goiter heart,” “thyrotoxic heart,” “thyroid heart,” “thyrotoxic myocarditis,” etc., have acquired established usage.

Many of the early writers did not distinguish the cardiac phenomena of hyperthyroidism from those encountered with large colloid goiters. Rose² advanced the belief that pressure of the enlarged thyroid gland upon the trachea, and upon the great vessels and nerves in the neck, brought about cardiac embarrassment. Thus arose the term “mechanical goiter heart.” The majority of the reports upon this condition have been based upon studies in Bavaria, or the Tyrol, where large colloid goiters are relatively common. Marine³ has also shown that hypertrophy of the heart and dilata-

tion of the great vessels frequently occur in animals with colloid goiters. Other observers⁴ have drawn attention to the increased vascularity of the thyroid gland in some types of goiter and have attributed the cardiac manifestations to overwork occasioned by an arteriovenous shunt.

That mechanical factors may be partially responsible for the cardiovascular phenomena in some instances of simple goiter must be admitted. That, however, they serve to explain the cardiac manifestations of hyperthyroidism is extremely difficult to accept in view of the following facts: (1) Cardiac enlargement, arrhythmia, or even myocardial insufficiency not infrequently occur in hyperthyroidism associated with a thyroid gland normal in size or only slightly enlarged, and (2) following subtotal thyroidectomy no immediate circulatory alterations occur such as are to be observed following closure of an arteriovenous aneurysm.

Krause,⁵ in a series of papers published between 1889 and 1899, drew particular attention to the "thyrotoxic heart." It has been assumed from isolated reports of degeneration of inflammatory myocardial lesions, discovered in the hearts of patients who died with hyperthyroidism, that the heart alone has been singled out for attack by some circulating poison. However, a study of the autopsy material at the Johns Hopkins Hospital by McEachern and Rake⁶ revealed that of 27 patients dying with hyperthyroidism the myocardium was normal in 14 instances and showed but slight alterations in 8 instances. Among the 5 instances in which profound changes were found in the myocardium there was coëxisting cardiac disease (syphilis, rheumatic endocarditis, etc.) in 3. These authors concluded that there was little evidence to be derived from studies of the morbid anatomy of the heart to support the view that the myocardium was attacked by a specific toxic substance in hyperthyroidism. They were, furthermore, unable to correlate the clinical symptoms in these cases with such structural changes as were observed in these hearts. The literature upon this subject is reviewed in their paper.

It is a very important fact, which should be emphasized, that the *degree* of intoxication will not alone explain the development of myocardial insufficiency in this disease. Indeed, in a fair proportion of the fatal cases the patients appear to perish in the flame of hyperthyroidism (*e. g.*, a postoperative crisis) without manifesting signs of heart failure. It has been pointed out elsewhere⁷ that in hyperthyroid individuals below 40 years of age myocardial insufficiency is almost invariably associated with preëxistent cardiac disease (rheumatic or, more rarely, syphilitic). In the decades above 40 the greater frequency of failure as a complication of hyperthyroidism is associated with three factors:

1. The greater incidence of so-called adenomatous goiter, characterized by exacerbations and remission over a period of years.

2. The natural diminution of the cardiac reserve which takes place with the years beyond 40 plus the occasional coincidence of rheumatic or hypertensive cardiac disease with hyperthyroidism at this age.

3. The coexistence in many patients of 50 years and over of arteriosclerotic heart disease.

A further point against the assumption of a specific destructive toxin acting upon the heart is the rapidity with which the most serious evidences of cardiac embarrassment may disappear, literally overnight, following relief of the hyperthyroidism by operation or during a remission brought about by iodine. The slower but equally striking disappearance of congestive heart failure that usually follows institution of these measures has been noted by Hamilton,⁸ Lahey,⁹ Levine¹⁰ and many others. Thomas,¹¹ indeed, is of the opinion that in most instances the heart returns to an entirely normal state following adequate thyroidectomy.

Hyperthyroidism can be produced with ease in animals and in the human being by the administration of thyroid gland, its active fractions or thyroxine. As in the spontaneous hyperthyroidism of the human being, tachycardia and overactivity of the heart are early and striking features. Taking advantage of this fact, a series of experimental studies has been carried out in this laboratory during the past 3 years. In 1929 Lewis¹² showed that the hearts and auricles of thyrotoxic rabbits continued to beat, when completely isolated, at a much faster rate than similar preparations from normal animals. (Fig. 1.) This was a constant and striking phenomenon and appeared to indicate a persistence of the "state of hyperthyroidism" in the isolated tissue. In a large number of such experiments Andrus and McEachern¹³ found that the average rate of the preparations from thyrotoxic animals was 56 per cent greater than that of the normal controls. In individual instances the former preparations not infrequently beat twice as fast as the controls. The accelerated rate showed no tendency to wear off during the period of observation which in several instances extended for 10 hours. This result was considered to indicate that some fundamental change in the metabolism of the cardiac tissue had been caused by the thyroxine. Yater,¹⁴ working independently has confirmed this observation, and has shown that the effect may persist for 12 days after the withdrawal of thyroxine. This point is of particular importance since it suggests that the degree of tachycardia of the isolated heart is proportional to the degree of hyperthyroidism in the intact animal. If the tachycardia were due to some specific toxic substance working damage to the myocardium the decrease in heart rate should not necessarily parallel the decreasing concentration of the toxic agent. This phenomenon appears, however, to be both quantitative and reversible for a particular animal and suggests that the effect is a metabolic one. Yater has

also shown that the idioventricular rate is enhanced in the isolated heart of a thyroxinized animal following section of the His bundle. Hitherto an attempt had been made to glean such evidence indirectly through the observation of a few cases of complete heart block to which thyroid had been administered. This subject is discussed in another place.¹⁵

Mann and his associates¹⁶ at the Mayo Clinic have extended this observation and have shown that following thyroid administration the tachycardia can develop in a normal heart which has been removed and grafted upon another animal. This fact again suggests that the tachycardia is due to a direct action of thyroxin on the muscle cells and not merely to a stimulation of nerve endings in the heart.

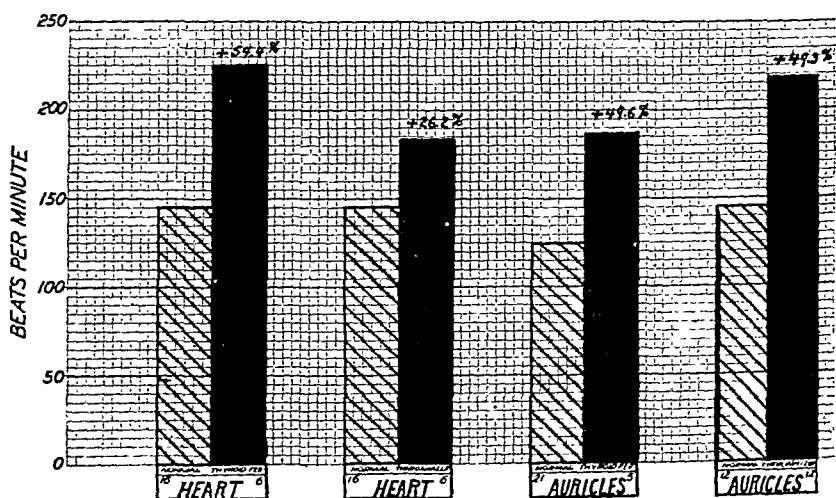


FIG. 1.—Comparison of the maximum rates of isolated hearts (Langendorff apparatus) and isolated auricles (Dale bath) of normal and thyrotoxic rabbits.

The conception that fundamental changes in the metabolism of the cardiac muscle may be at the root of the matter has received impetus from recent investigations of the lactic acid metabolism in patients with hyperthyroidism. A number of observers^{17,18,19} have shown that the lactic acid in the blood of hyperthyroid individuals rises to a much higher level following muscular work and falls much more slowly when the work is discontinued than is the case in normal individuals. Furthermore, König²⁰ has shown that hyperthyroid animals die in convulsions following intravenous injections of calcium lactate in doses that are borne by normal animals without symptoms. That rigor mortis occurs more rapidly in thyrotoxic than in normal animals has been noted by Hashimoto²¹ and by Rake and McEachern.²² It has long been known that thyrotoxic animals are less able than normal animals to withstand reductions in the partial oxygen pressure of their environment.

It seemed important to repeat, upon isolated cardiac tissue, some of the experiments that had previously been performed upon intact thyrotoxic animals. For this purpose the auricles from a normal and a thyrotoxic animal were removed simultaneously, set up in oxygenated Ringer-Locke's solution (37°C.) and made to register one above the other on a revolving smoked drum. When intact hearts were used they were perfused by the Langendorff method. It was found¹² that no significant changes were produced in the rate and amplitude of contraction or the coronary outflow in these preparations by the addition of thyroxin, desiodothyroxin or iodids in varying concentrations. Epinephrin brought about a greater *absolute* acceleration in rate of beat in the auricles of the thyroxinized animal than in the normal, but the same *percentage* acceleration in both. It was further observed¹³ that upon interruption of the oxygen supply (Fig. 2) or upon introduction of isotonic solutions of sodium lactate into the bath, the auricles from thyrotoxic animals were affected more quickly and more profoundly than the normal



FIG. 2.—Simultaneous tracings recorded by auricles of normal (below) and thyrotoxic (above) rabbits. Effect of withdrawal of oxygen.

auricles. In like manner the former preparations recovered much more slowly upon reestablishment of the original conditions of the experiment.

These findings further suggested that the auricles from thyrotoxic animals were more dependent than were the normal controls upon their contemporary oxygen supply, which in turn suggested that their rate of oxygen consumption might be increased beyond the normal. It also seemed possible that these preparations were either elaborating lactic acid at a faster rate or were less able to oxidize it or get rid of it by diffusion than the normal auricles.

By direct volumetric measurements it has been shown²³ that the isolated beating auricles from thyrotoxic guinea-pigs consumed from 7 to 20 per cent more oxygen per gram of tissue than auricles of similar weight from normal animals. (Fig. 3.) Lewis and Dock²⁴ using the heart-lung preparation of the rat have recently confirmed these results. Whether the increased rate of contraction in the preparations from thyrotoxic animals is entirely responsible for the

increased oxygen consumption is still a matter of conjecture. The fact is that both an increase in rate of beat and in oxygen consumption occur in the isolated heart of the thyroxinized animal.

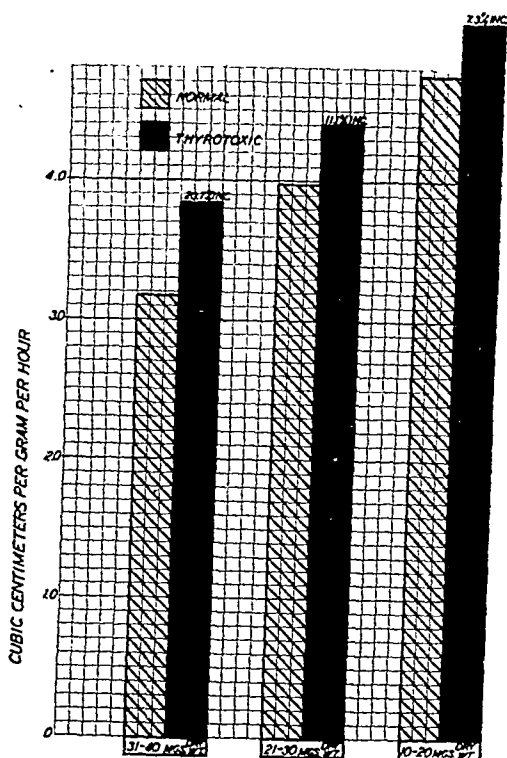


FIG. 3.—Comparison of the oxygen consumption of isolated beating auricles from normal and thyrotoxic guinea pigs, according to weight groups (Warburg apparatus).

Direct chemical estimations have also been made²⁵ of the lactic acid, glycogen and total base in cardiac muscle from normal and thyrotoxic rabbits. The results are shown in Table 1:

TABLE 1.—LACTIC ACID, GLYCOGEN AND TOTAL BASE IN MUSCLE OF NORMAL AND THYROTOXIC RABBITS IN MILLIGRAMS PER CENT.

	Cardiac Muscle		Skeletal Muscle	
	Normal	Thyrotoxic	Normal	Thyrotoxic
Glycogen	288.0	166.0	396.0	272.0
Lactic acid	31.6	50.5	84.4	113.4
Total base	132.6	125.9	149.6	150.8

The lactic acid content of the cardiac muscle is seen to be almost doubled in the thyrotoxic group. The glucose and total base have undergone no significant change. A similar depletion of the glycogen of skeletal muscle in thyrotoxic animals has been noted by previous observers.^{26*}

* These authors (Dock, W., and Lewis, J. K., *J. Physiol.*, 1932, 74, 406) state that the increased oxygen consumption of the heart-lung preparations from thyroid-fed rats can be entirely accounted for by the increased rate of beat and the weight of such hearts.

These experiments appear to show that the tachycardia of hyperthyroidism and possibly other and more serious phenomena are related to the direct *metabolic* action of thyroxin or its products on the myocardium. The application of the above facts to hyperthyroidism in the human must be apparent.

In short, it appears that the cardiac tissue shares in the metabolic upheaval characteristic of this disease. In addition there falls upon the myocardium the burden of the increased circulatory demands of the entire organism, the metabolism of which is elevated. These two factors combine to bring to the fore the cardiac manifestations of hyperthyroidism; in individuals whose circulatory reserve has been diminished by age or by organic cardiac disease they may result in myocardial failure.

That prolonged hyperthyroidism results in some degree of cardiac hypertrophy seems to be well established. Thus among the 27 cases reviewed by McEachern and Rake there was moderate cardiac hypertrophy in 16. However, hypertrophy does not indicate myocardial damage; much less is it due to the action of a specific myocardial poison. In this instance it is to be attributed to the burden of an increased circulatory minute volume.²⁷ There is, indeed, little evidence that the heart is permanently damaged. How much functional impairment may be produced by a protracted siege of this disease is a question yet unsettled.

Conclusion. It is, perhaps, the most accurate, and certainly the most optimistic attitude, to look upon the heart in hyperthyroidism as suffering from its own accelerated metabolism and from the load thrown upon it by the metabolism of the body as a whole. From both of these burdens it can, happily, be relieved by relief of the hyperthyroidism.

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THE MANAGEMENT OF THE DECOMPENSATED CARDIAC INVALID.

I. ONE HUNDRED CASE RECORDS ANALYZED FROM THE STANDPOINT OF THE INDIVIDUAL PATIENT.

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The medical service of the Montefiore Hospital presents an excellent opportunity for the study of the management of the decompensated cardiac invalid. One hundred of these patients

are usually resident in the hospital. Of these, between 15 and 20 are children who have been studied by Schwartz¹ and his coworkers, and will not be included in the present analysis.

We have reviewed an unselected group of 100 consecutive histories. No protocol was arranged for this work. No special investigations were planned. The patient was treated as an individual according to the therapeutic problem which presented itself. Our purpose has been an analysis, *a posteriori*, of the various therapeutic measures employed.

Type of Material. For the most part, our patients have passed through the acute phases of their disease. In most instances the victims of rheumatic fever no longer presented any evidence of activity of their infection. In the arteriosclerotic group, the acute episodes, such as thrombosis and embolism, were part of the past history. The problem was sharply limited to the management of the advanced and decompensated cardiac invalid, who had already passed through the active stages of his illness, and who had failed to respond to home or ambulatory treatment.

Classification of Material. (a) Forty-three of these patients had carditis as the result of a previous infection with rheumatic fever. (b) The second large group of 54 presented various manifestations of degenerative arteriosclerotic phenomena. This latter group was again subdivided. There were 2 with generalized arteriosclerosis; 25 with uncomplicated hypertension of the greater circulation; 4 with hypertension of the lesser circulation; and 23 with hypertension, who also presented electrocardiographic changes suggesting arborization block or lesions of the coronary vessels.

(c) Of the 3 remaining patients, not classified, 1 had a ball-valve tumor of the auricle, the second an advanced nephritis, and the third a congenital cardiac lesion.

Vital Statistics. In the rheumatic group, the females predominated by 2 to 1, whereas the proportion was exactly reversed in the arteriosclerotic group. The patients with rheumatic fever were younger, though 14 per cent had survived beyond the fiftieth year. The average age of the rheumatic women was 38, and of the men 35.

In the arteriosclerotic group the men averaged 54 and the women 62 years of age. The breakdown of the men occurred at a period almost a decade earlier than the women and resulted probably from the greater wear and tear in the struggle for existence. This was further emphasized in the subclassification of the arteriosclerotic group, where the preponderance of males increased with the severity of the complication.

Valvular Defect. The mitral valve was involved in each of the rheumatic group, and in addition 68 per cent had aortic valvular disease, and 16 per cent a combination of mitral, aortic and tricuspid endocarditis.

In the arteriosclerotic group, only 10 per cent had evidence of

Two patients had a sufficient diuresis from urea so that no other medication was necessary, and no reaccumulation of fluid occurred.

Eighteen patients had a successful diuresis with extraordinary clinical improvement as the result of the administration of salyrgan. The salyrgan was supplemented three times by the mechanical removal of the fluid, six times by the simultaneous oral administration of urea, once by both urea and the mechanical removal of fluid, and twice by digitalis.

C. The Decompensated Rheumatic Cardiac Invalid With Auricular Fibrillation. Thirty-two patients, with valvular defects as the result of rheumatic fever, presented an auricular fibrillation. In 2 instances physiologic rest was sufficient to restore compensation.

In the remaining 30 cases, the effect of digitalization was absolutely specific. In 9 patients, no other form of therapy was employed, and in another the digitalis was supplemented only by a thoracentesis.

In 20 instances the diuretic effect of salyrgan was a potent factor in the restoration of the circulation. In 8 of the last 20 patients, the digitalis and the salyrgan were supplemented by mechanical measures in 3 instances, and by the continual administration of either urea or the ammonium salts in the other 5.

D. The Arteriosclerotic Decompensated Cardiac Invalid With Auricular Fibrillation. Twenty-nine arteriosclerotic patients had cardiac insufficiency with permanent auricular fibrillation. Twelve had hypertension of the greater, and 4 of the lesser circulation. Thirteen had electrocardiographic evidence of myocardial damage, either bundle-branch block, or changes in the *S-T* interval, suggesting coronary damage.

Two patients responded to physiologic rest without any specific therapeutic measure.

Twenty-two of this group were restored to compensation as the result of digitalization. Eight patients needed digitalis alone, and 2 others required only urea in addition.

The next group of 12 patients required salyrgan, as well as digitalis, and half of these responded to the administration of these two drugs alone. In addition to the salyrgan and digitalis, the remaining 6 patients required either mechanical removal of the fluid, or the enhancement of the salyrgan effect by the oral administration of urea or ammonium salts.

Five patients were unaffected by digitalization, but did respond favorably to salyrgan. These patients all presented advanced cardiac disease, with electrocardiographic evidences of coronary lesion.

Summary. 1. The records of 100 decompensated cardiac invalids have been summarized, and the therapeutic regimen noted.

2. Eight patients were restored to compensation by physiologic rest and dietotherapy.

3. Mechanical removal of fluid from the serous cavities was practiced in 14 of the group.

4. Fifty-six patients were specifically benefited by digitalis and all but 4 in this group had auricular fibrillation.

5. Sixty-four patients, edematous despite physiologic rest, dietotherapy and digitalization, were relieved by the administration of salyrgan with or without the simultaneous administration of urea and the acid salts. Five patients responded by diuresis to urea alone.

6. The four cardinal steps in the management of the decompensated cardiac invalid are: (1) Physiologic rest and dietotherapy; (2) mechanical evacuation of fluid from the serous cavities; (3) digitalization and (4) the use of the diuretics.

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THE MANAGEMENT OF THE DECOMPENSATED CARDIAC INVALID.

II. EFFECTS OF SPECIFIC MEDICATION.

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IN the previous paper¹ we have discussed the management of 100 cardiac invalids from the standpoint of the individual patient. Four important principles stood out in this analysis: (1) Physiologic rest, including dietotherapy; (2) the mechanical evacuation of fluid from the serous cavities; (3) digitalization; (4) the use of the diuretics.

In this paper we shall discuss each of these cardinal principles with special emphasis upon the clinical pharmacology of the specific drugs.

Physiologic Rest. Institutionalization and dietotherapy are the prime factors in securing physiologic rest. The admittance of the cardiac invalid to the institution is a nonspecific form of therapy whose importance cannot be overestimated. The patient is no longer a drain upon the family budget. As a general rule he is removed from the unhealthy and squalid surroundings of a metro-

politan tenement and transplanted to the relative quiet, cleanliness and comfort of a hospital bed. In the place of haphazard and infrequent medical visits, he is seen several times daily by trained observers. The well-meaning but amateur brand of home nursing is replaced by skillful professional care.

Sedatives and hypnotics are liberally employed during this period. They have no deleterious effect on the circulation, even when given in large doses, and they do much to relieve the circulatory load by inducing rest and sleep. As a result, an extraordinary change for the better is a common experience and we attempt to introduce no specific form of therapy until the effects of institution-alization can be evaluated.

Dietary regulation is as important as it is simple. The weight of the patient is the only observation required. In adult patients, gain in weight almost invariably means the retention of water, and loss of weight is accompanied by, or the result of, diuresis. Restrictions are placed upon water, salt, and total calorie intake. For the first 2 days the time-honored Karell diet of 1 quart of milk and soda crackers is of prime importance. It is also useful once a week as a prophylactic after compensation has been restored. In the mildly decompensated case, full diet with limitation of fluids to 1500 cc. may usually be employed as a routine. The more severely decompensated patients may have to suffer a reduction in their fluid intake to 1200 cc., or even 1 liter. If they still retain water on this diet, the salt-poor regimen must be prescribed.

Obese patients, particularly those with hypertension, are placed on mixed diet with calories limited to 1500.

In our series 8 patients were restored to compensation by physiologic rest and dietotherapy.

Mechanical Measures. Fourteen patients had paracentesis abdominalis or thoracentesis. The hope that fluid will absorb as the result of rest or specific therapy is usually not fulfilled, and its immediate evacuation is a much wiser therapeutic policy. The patient should receive a liberal dose of morphin by hypodermic at least 10 minutes before the expected tap. The fluid is withdrawn slowly. It is unwise to take off more than 500 or 700 cc. from the chest. The abdomen, however, may safely be tapped dry. Tight pressure should be exerted during and following paracentesis. Adequate digitalization, or frequent doses of salyrgan, may occasionally prevent the reaccumulation of this fluid. If the fluid reaccumulates it must be mechanically removed again.

Digitalization. Seventy-nine patients received digitalis (Table 1.) Twenty-two of these had sinus rhythm; 9 in the rheumatic and 13 in the arteriosclerotic group.

In the rheumatic group, 7 had no appreciable effect, while 2 were damaged. In none of this group was digitalis of the slightest efficacy.

TABLE 1.—EFFICACY OF SPECIFIC THERAPEUTIC DRUGS IN TREATMENT OF DECOMPENSATED CARDIAC INVALID.

	Sinus rhythm.		Auricular fibrillation.		
	Rheu- matic.	Arterio- sclerotic.	Rheu- matic.	Arterio- sclerotic.	Total helped.
Digitalis:					
Toxic	2	1	0	1	
No effect	7	8	0	4	
Useful	0	4	30	22	= 56
Not used	2	12	2	2	
Urea:					
Diuretic	0	7	3	4	
Prevents reaccumulation of edema	2	3	3	3	= 25
No effect	2	3	7	7	
Not used	7	12	18	15	
Salycrgan:					
No effect	1	1	0	2	
Toxic	1	0	0	0	
Diuretic	9	18	20	17	= 64
Not used	0	5	12	10	

In the arteriosclerotic group with sinus rhythm, 8 were unaffected by digitalis, 1 patient was poisoned, and 4 had a successful therapeutic result. One of this last quartet was admitted in pulmonary edema, and experienced both a pulse slowing and a diuresis. The other 3 had a moderate diminution in the pulse rate, but required diuretics in addition. We were thoroughly convinced that the improvement in these 4 patients was due to the digitalis, at least in part.

In both the rheumatic and arteriosclerotic groups with auricular fibrillation the result differed strikingly from those with sinus rhythm. (Table 1.) In 52 of the 61 fibrillators, digitalis proved extremely efficacious. The result was independent of the etiology of the cardiac decompensation, the valvulitis, the sex or age of the patient, the degree of decompensation, or the presence or absence of hypertension. The 9 fibrillators who did not experience a favorable response were all the victims of a process so advanced as to preclude any possibility of therapeutic result. In these patients, as the result of repeated cardiac insufficiency, the myocardium gave evidence of either fibrosis or myelomalacia.

An accurately assayed tincture of digitalis (1 cc. = 1 cat unit) was used almost exclusively. In a few instances where vomiting had occurred as a result of salicylism or chronic passive congestion of the stomach we gave the leaf of digitalis in rectal suppositories. Though we were dealing with severe and advanced cases, we found no indication for the intramuscular or intravenous administration of the drug and we believe that form of therapy is greatly to be discouraged.

Idiosyncrasy to digitalis was not encountered in this series, nor have we experienced it during a long experience with the drug. One woman, who insisted that digitalis caused immediate vomiting,

also vomited when she was given a neutral green tincture under the guise of tincture of digitalis.

Concerning dosage, we are convinced that no rule of thumb can replace careful and frequent clinical observations. It is impossible to gauge the amount of the drug required by *a priori* reasoning. It is not necessary to saturate the patient with digitalis in order to obtain a therapeutic result. Indeed, in many patients there is a wide gap between the therapeutic dose and saturation. (Table 2.)

TABLE 2.—DIGITALIS DOSAGE.

Patient.	Pulse rate.		Total dose.	Span.	Saturation, amount.	Corrected, amount.	Error, per cent.
	Before.	After.					
I. L.	150	72	48	11	25	35	+40
M. C.	88	86	16	4	21	13	-40
E. W.	104	68	29	6	20	23	+14
R. S.	104	62	31	6	19	25	+33
B. S.	104	65	13	6	16	7	-50
D. S.	110	88	14	7	15	6.5	-50
E. W.	108	80	29	5	20	25	+25
A. S.	150	84	13	4	17	10	-40
J. K.	104	84	10	1	17	10	-40
M. R.	105	68	36	13	20	16	-20
D. S.	98	80	24	9	21	11.5	-45
A. S.	104	86	16	3	15	15	

All patients were in rheumatic group with auricular fibrillation. Total dose is in cubic centimeters of standardized tincture. Span in days. Saturation amount calculated by multiplying weight minus edema by 0.15.⁴ Corrected amount calculated by subtracting from actual amount administered the sum of the excretion (figured at 1.5 cc. per day)⁵ times the span minus 2 (no excretion for first 2 days). Error obtained from last 2 figures.

Wherever possible, no digitalis is prescribed until the patient has been observed at least 48 hours. This preliminary observation serves two purposes: (1) The evaluation of the efficacy of the nonspecific measures, such as rest, water and fluid restrictions, and sedatives; (2) the excretion of any digitalis given before admission.

It is our custom to order 4 to 8 cc. of the tincture the first day that the digitalis is administered. Standing orders for the administration of digitalis should not be given. The patient must be seen at least once and preferably twice a day during the active period of digitalization. In those patients with auricular fibrillation, from 2 to 4 cc. are ordered daily until the pulse rate approximates 75 to 80, or unless the patient experiences toxic symptoms, such as gastrointestinal distress or a new cardiac irregularity. Under such circumstances, the drug is stopped for 24 hours and then 1 to 2 cc. daily is prescribed as a maintenance dose. This is continued indefinitely, and increased if the pulse rate increases, or stopped for 24 hours if the rate becomes too slow or toxic symptoms develop. In the presence of sinus rhythm the drug is discontinued at the end of a week if no therapeutic effect is seen, but if the patient is benefited the dosage is maintained exactly as in auricular fibrillation. Despite the rarity with which a favorable outcome is experi-

enced in patients with sinus rhythm, we give every decompensated patient the benefit of digitalization and, even in the face of failure, repeat the course of digitalis every few months as a therapeutic test.

In the more favorable cases under digitalis, the pulse rate slows and there is a diuresis accompanied by loss of weight, dyspnea lessens, and paroxysmal nocturnal attacks of pulmonary edema may be prevented. Where pulse slowing is not accompanied by diuresis the digitalis may have to be supplemented by the mechanical removal of fluid from the serous cavities, or the exhibition of the diuretics.

The digitalis-like bodies have been tried in those decompensated cardiac invalids who fail to improve with digitalis. At the present time the only representative of this group that is commonly encountered in clinical practice is squill. Convallaria, apocynum and spartein seem to have been justifiably dropped out of the therapeutic armamentarium.

In a group of 12 patients we administered squill as scillaren. In none of these was any unusual circulatory benefit derived from the scillaren. In four instances, however, there may have been a slightly greater diuresis than with digitalis. This was offset, however, by the fact that while digitalis produced nausea in only one of this group, scillaren caused nausea five times, and diarrhea once.

Our experience indicates that the pharmacology of the digitalis group may be simplified to a great extent by eliminating all of the preparations other than the tincture and the leaf of digitalis, and by administering these only by the oral or rectal route. The dosage cannot be estimated by any *a priori* calculation. This opinion bears out the original writing of Withering who said, "Let the medicine be continued until it acts either on the kidneys, the stomach, the pulse or the bowels—let it be stopped at the first appearance of any of these effects."

Diuretics. Specific drug treatment for the compensated cardiac invalid is wholly summarized by digitalis and the diuretics. In our experience the problem of diuretics may be simplified by eliminating all but the saline preparations (urea and the acid salts) and the mercurials, such as salyrgan.

Urea. Urea is made up by adding, to 1 pound of the salt, water to make a quart. Three tablespoonfuls of the solution 3 times a day will give about 70 gm. The evil taste may be disguised somewhat by tomato or fruit juices. Forty-eight of our patients received urea. (Table 1.) In 19 it proved to be of no value and in 3 of only questionable efficacy. It was useful in about one-fourth of the whole group. In these last cases the urea was actively diuretic in 14 instances. Its use was accompanied by a loss, and its discontinuance was followed by a gain, of weight. Illustrating this, J. M. lost 18 pounds during the first five weeks that he received urea, and B. P. gained 27 pounds in 3 months following the cessation of

urea. In 11 instances the urea, while not actively diuretic, held the loss of weight resulting from the mercurial diuresis and thus diminished the number of salyrgan injections.

In several instances urea has been administered over a period of years despite elevation of the blood-urea figures to as much as 105 mg. per 100 cc. We have seen no untoward reaction other than an occasional urea rash, which disappeared when the drug was discontinued.

Many of our patients felt so strongly that their well-being depended upon the administration of urea, that considerable agitation occurred in one of the wards when we wished to discontinue the drug for a few days as an experiment.

Acid Salts. The acid salts (ammonium chlorid or carbonate and calcium chlorid) are given in dosages of 10 gm. daily. They may be administered in capsules or in large chocolate-coated tablets. They are indicated when edema persists, despite digitalization, rest, and the limitation of fluids and salt in the diet. In conjunction with the mercurial diuretics they tend to promote diuresis and prevent the reaccumulation of fluid.

Thirteen of our patients were benefited by their use. In only 2 of these instances was the salt actively diuretic, in others it either increased the yield from the mercury or prevented the reaccumulation of fluid after the salyrgan.

Mercurials. Second only to digitalis in the management of the cardiac invalid is the importance of the mercurial compounds. Our personal preference is for salyrgan, which can be administered intramuscularly or intravenously in doses of 1 to 2 cc. Injection of this extremely irritant compound requires the most meticulous care, for a careless introduction may be followed by a cellulitis and slough lasting several months, while the intramuscular injection is usually painful, may result in a sterile abscess, and if injected in the vicinity of a nerve will cause degeneration. If it can be successfully practised, the intravenous route is to be preferred. To insure safety, blood should be drawn up into the syringe before the injection; the drug should be administered slowly and discontinued if the patient complains of the slightest pain, or if any induration is visible or palpable. Blood should be withdrawn from the vein before the needle is taken out. Where repeated injections must necessarily be given, the veins will sooner or later sclerose. The intramuscular injections should be followed by the injection of 0.5 cc. of air, so that the mercury is not deposited along the track of the needle during its withdrawal.

Sixty-four of our patients were dependent upon salyrgan (Table 1). The extraordinary value of this preparation can be seen when it is compared to digitalis, which was useful in only 56 patients. Our 64 patients received a total of 847 injections, and averaged 14 each. One man had had 150 injections scattered over a period of 3 years. The average yield from salyrgan was the equivalent to 4 to 5 pounds

loss in body weight. In the presence of a great deal of edema, the first injection caused a loss of weight up to 10 pounds, and on a few occasions 12 to 13 pounds. In 43 instances the salyrgan needed no supplementation. Eight times, however, its use was enhanced by urea and thirteen times by one of the acid salts. In these instances the salts either increased the salyrgan yield or prevented the reaccumulation of fluid following the salyrgan diuresis, so that injections of the mercury could be separated wider apart. In ten instances, most of which were in the group of patients with sinus rhythm, the diuresis following salyrgan was alone sufficient to restore compensation. In 1 patient a hydrothorax receded.

In addition to the measurable evidences of diuresis, such as increased urine output and loss of body weight, 23 patients experienced a marked relief from dyspnea and 2 from pain in the right upper quadrant as the result of a congested liver. There were several instances of marked reduction in the number and severity of the attacks of paroxysmal nocturnal dyspnea often erroneously called "cardiac asthma." This condition is wholly unrelated to asthma and should never be treated with antispasmodics, particularly adrenalin. Actually, these are attacks of paroxysmal pulmonary edema and respond, as edema elsewhere, to fluid and salt restriction, digitalis, and the diuretics, particularly salyrgan.

The toxicity of salyrgan is almost wholly limited to its local reaction. We do not hesitate to employ the drug in the presence of marked albuminuria, even when this is marked or accompanied by casts or an occasional red cell. We have yet to see clinical evidences of a significant amount of kidney damage following the use of the mercurial diuretics. We do not hesitate to repeat the dose in 4 or 5 days, but we prefer to wait a week if that is possible.

Bismuth. Despite the wholly satisfactory use of salyrgan, we were impelled to study the efficacy of bismuth sodium tartrate² as a diuretic. Eleven patients previously treated with salyrgan were given bismuth. Whereas the average yield with salyrgan had been 4.6 pounds, it was 0.8 pound with bismuth. (Table 3.)

TABLE 3.—COMPARISON OF DIURETIC ACTIONS OF SALYRGAN AND BISMUTH SODIUM TARTRATE.

Patient.	Diagnosis.	Effect of bismuth.	Effect of salyrgan 3 days later.
N. S.	CRCVD	Gained $\frac{1}{4}$ lb.	Lost 5 lbs.
H. H.	"	Lost $\frac{1}{2}$ lb. in 2 days	Lost 6 lbs.
I. G.	"	0	Lost 6 lbs.
N. P.	"	0	Lost 8 lbs.
N. N.	"	Lost 7 lbs. in 7 days	Lost 3 $\frac{1}{2}$ lbs. in 1 day
R. D.	"	Lost 2 lbs.	Lost 2 lbs.
A. G.	"	0	Lost 4 lbs.
M. M.	"	0	Lost 8 lbs.
L. S.	"	0	Lost 2 lbs.
H. H.	CVR	Gained 1 $\frac{1}{2}$ lbs.	Lost 2 lbs.
M. K.	"	Lost $\frac{1}{2}$ lb.	Lost 4 lbs.

Purins. The purin diuretics enjoy a great popularity. With one exception, not a single patient in this group had a significant diuresis from any member of this group, which included theobromin, diuretin, caffein and theocalcin. Because of the enthusiastic reports of the diuretic action of theocalcin,³ we gave 5 of our patients, usually controlled by urea or ammonium chlorid, 1.5 gm. daily, and 4 of them gained weight on the purin and lost weight when the saline diuretic was resumed.

Cardiac Stimulants. The omission of any previous mention concerning the most popular of the cardiac drugs requires comment. In the records of the helpful therapeutic measures, caffein, strychnin, camphor, and adrenalin are conspicuous by their absence. In the management of the chronic decompensated cardiac invalid, these drugs are definitely valueless. Invariably, however, discussion of their use arises during acute decompensation or when death is imminent. Under these latter circumstances, no accurate evaluation of therapeutic procedures is possible and one can only express a personal opinion. For ourselves we are convinced that camphor is inert and may cause embarrassment by the production of a marked local induration. Strychnin has no appreciable effect on the circulation and may cause toxic symptoms in the realm of the nervous system. Adrenalin is absolutely contraindicated. If given in effective doses, particularly in so-called "cardiac asthma," the sudden rise in blood pressure has frequently been sufficient to overwhelm the circulation and result in sudden death. Fortunately in most instances it is given subcutaneously or intramuscularly and is not sufficiently absorbed, particularly with chronic passive congestion, to cause any response. Caffein may be employed if the patient is unconscious. Under any other circumstances the cerebral stimulation and the resulting anxiety far overshadow any circulatory effect. Given to the conscious patient it will cause distress both to the sufferer and his attendants.

The administration of oxygen is frequently helpful in acute decompensation and can be carried on by a nasal catheter if more elaborate apparatus be not available. Liberal doses of morphin and other sedatives do much indirectly for the circulatory system by allaying anxiety and producing sleep.

Summary. 1. Drug therapy is indicated in the cardiac invalid who remains decompensated despite physiologic rest, dietotherapy and the mechanical evacuation of fluid from the serous cavities.

2. Digitalis is invaluable in those patients who present auricular fibrillation. Its clinical pharmacology is discussed.

3. Diuretics are equal in importance to digitalis in the management of the decompensated cardiac invalid. Their use is independent of the cardiac rhythm. Their pharmacology is discussed and the preparations are narrowed down to three—urea, the acid salts and salyrgan.

4. This list completes the list of specific drugs useful in the management of the decompensated cardiac invalid.

5. The list of other popularly used remedies is discussed and their use criticized. Included in this category are the purin diuretics, bismuth subtartrate, the alleged circulatory stimulants (camphor, strychnin, caffein and adrenalin), and the antispasmodics.

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EXPERIMENTAL CHRONIC HYPERPARATHYROIDISM.*

II. OSTEITIS FIBROSA PRODUCED IN RATS.

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SANDSTRÖM³¹ discovered the parathyroid glands in 1880, but the importance of these structures was not realized until Gley,^{16,17} in 1891, showed that the tetany which occasionally followed thyroidectomy was not due to removal of the thyroid but to the accompanying parathyroidectomy. Hypoparathyroidism has been recognized as a clinical problem since that time.

Hyperparathyroidism was probably suspected as early as 1904 by Lundborg²⁸ and later by Chvostek,⁷ but it was not until 1926 that it attracted much attention. A series of events prepared the way for its recognition. Hypertrophy of the parathyroids was observed in association with certain diseases of bone, such as osteomalacia, rickets, osteogenesis imperfecta and most frequently osteitis fibrosa. Hoffheinz¹⁹ and Barr and Bulger⁴ give reviews of the literature between 1900 and 1929, and report a total of 76 instances of this association. There should now be added at least 12 others which include 3 cases reported by Barr and Bulger,⁴ 4 by Hunter^{20,21} and 1 each by Compere,¹³ Gold,¹⁸ Eggers,¹⁴ Lanz²⁷ and Ask-Upmark.² Askanazy¹ attributed a pathogenic rôle to this hypertrophy as early as 1904. Erdheim¹⁵ regarded it as an inadequate attempt at compensation. Of primary importance was the preparation by Collip of an extract of the active principle of the parathyroids,^{8,9,11,12} and the observation of Mandl²⁹ that removal of a parathyroid tumor in a case of osteitis fibrosa was therapeutically beneficial. Mandl had previously transplanted human parathyroid glands into the abdominal wall of this patient with resulting aggravation of symptoms,

* The expenses of this research were met from the John D. Hertz Fund.

and this had aroused the suspicion that parathyroid overfunction was at fault, rather than underfunction. The operative removal of tumors of the parathyroid has since been performed in a number of clinics with results in osteitis fibrosa like those of Mandl.

TABLE 1.—DIAGNOSTIC FEATURES OF HYPERPARATHYROIDISM AND OSTEITIS FIBROSA OSTEOPLASTICA.

I. More frequent findings:	II. Less frequent findings:
1. Increased urinary excretion of calcium.	1. Bone deformities.
2. Negative calcium balance.	2. Multiple cysts.
3. Hypercalcemia.	3. Pathologic fractures.
4. Hypophosphatemia.	4. Giant cell tumors of bone.
5. Parathyroid hypertrophy or hyperplasia.	5. Impaired kidney function.
6. Rarefaction of bones.	
7. Decreased muscular response to stimulation.	
8. Muscular weakness and hypotonia.	
9. Muscle and bone pains.	
10. Anemia.	

The criteria of osteitis fibrosa osteoplastica (von Recklinghausen) are listed in the accompanying table. The purpose of my investigation was to determine whether the experimental reproduction of a chronic state of hyperparathyroidism by repeated injections of parathormone would reproduce this disease or result in the development of some other skeletal abnormality such as osteomalacia, rickets, osteogenesis imperfecta or multiple myeloma. Each of these, as has been stated, has been associated occasionally with parathyroid hypertrophy.^{4,26}

Waltner³⁴ attempted to prove that hyperfunction of the parathyroid glands was responsible for rickets. He experimented with young white rats, using three diets. In one of these the calcium and phosphorus contents were normal, in one phosphorus was deficient, a decidedly rachitic diet and in one calcium was deficient, a somewhat rachitic diet. Each rat received 20 units a day of Collip's parathormone for from 8 to 18 days. With the normal diet an osteoporosis was evident, but no rickets. With the deficient diet both rickets and osteoporosis developed. In no case did the controls receiving the normal diet develop rickets, but some of the controls on the deficient diet did. Waltner concluded that while parathormone would wash calcium from the bones of young rats it did not produce rickets.

Bauer, Aub and Albright⁵ gave parathormone to rabbits, cats and rats and studied its effects by gross examination and with roentgenograms. A study of the blood serum calcium was included. Their rabbits revealed a reduction in the number of trabeculae but no gross changes of the cortex of bones. Histologic examinations were not made. In growing kittens no greater reduction of trabeculae was observed than occurred in the course of normal bone

growth. The skeletons of the rats appeared, by roentgenogram, to be much denser and shorter than those of their control siblings, and the number of trabeculae was found to be increased on gross examination of the sectioned bones. A rise in serum calcium was not observed in cats or kittens, but a slight rise was secured with rats and rabbits.

Jaffe, Bodansky and Blair^{22,23} have recently reported a very complete study of the effect of repeated injections of parathormone in dogs and guinea pigs. The histologic examination of the skeletons of their animals revealed lesions that are characteristic of osteitis fibrosa. In most cases the serum calcium was increased and the serum phosphorus decreased by the parathormone injections, but skeletal lesions occurred without hypercalcemia or hypophosphatemia.

Numerous other reports of parathormone injections in animals and man are contained in the literature, but as far as has been ascertained those referred to are the only ones in which attention has been directed to lesions of the bones.

My preliminary experiments,²⁴ which resulted in the production in rats and in puppies of bone lesions characteristic of osteitis fibrosa were completed before the work of Jaffe, Bodansky and Blair was brought to my attention. A chronic state of hyperparathyroidism was produced in rats and dogs by repeated injections of parathormone and the skeletal abnormalities were studied grossly, roentgenologically and microscopically. The effect of this procedure on serum calcium and phosphorus and metabolic balances of calcium, phosphorus and nitrogen were studied in separate experiments conducted on man, as previously communicated.²⁶ The data obtained with dogs will be reported later. The observations with rats is the subject of the present paper.

Methods. White rats from 6 to 12 weeks old were used, young animals being chosen for the reason that growing bones would probably reveal more striking abnormalities. Steenbock's normal rat diet was given. This consisted of yellow cornmeal, 76; linseed meal, 16; crude casein, 5; ground alfalfa, 2.5; sodium chlorid, 0.5 and calcium carbonate, 0.5 per cent. Distilled water was supplied for drinking. The food and water were kept in the cage at all times. This diet was started 1 or 2 weeks before treatment began. A number of animals received varying amounts of parathormone in the effort to arrive at a satisfactory dosage, the dose finally adopted being one of from 10 to 20 units injected subcutaneously. Animals were started with 10 units, this was increased after about 5 days to 15 units, and after a week or 10 days to 20 units. Twenty days was about the average duration of an experiment, although some rats received parathormone for as long as 43 days. Control litter mates were maintained on the same diet and under the same conditions as injected animals.

In certain cases when definite skeletal abnormality had become visible grossly and by roentgenograms, the medication was discontinued to observe the recovery. The diet in these cases was not altered.

Roentgenograms of the entire skeleton of all animals were made at death or at killing. In several instances periodic roentgenograms were obtained during the course of the experiment.

TABLE 2.—SOME RESULTS OF PARATHORMONE ADMINISTRATION TO RATS.

Rat No.	Sex.	Days on experiment.	Parathormone administration.		Gross observations. †	Roentgenological observations. ‡	Microscopic observations. ‡
			Dose* in units.	Total units.			
1 . .	M	42	10 ³³ (42)	330	Toes on left forefoot drawn like clenched fist; ³ does not bear weight on left foot; growing well; condition remained good throughout; killed ¹²	++ Long bones moth-eaten appearance at epiphyses; suggestion of kidney outline	+++ + Decalcification, resorption of cortical and trabecular bone, fibrous replacement, bone and marrow, cyst formation, giant cells, osteoid tissue; one area of highly vascular fibrous tissue.
2 . .	M	42	10 ⁷ (⁹) 20 ³ 15 ²² (³⁰)	475	Agglutination of eyelids, red material around eyes like dried blood; ¹¹ eyes cleared; ¹² condition good; ¹² beginning bowing and knobbing; ¹² killed ¹²	+ Rarefaction of tail vertebrae; slight rarefaction of long bones	+++ Decalcification, bone resorption, bone and marrow fibrous, cysts, giant cells, osteous tissue.
3 . .	F	42	10 ⁷ (⁹) 20 ¹ 15 ²² (²⁷)	480	Condition good; no appreciable change at end of experiment; killed ¹²	++ Rarefaction of long bones; curvature of left tibia	+ Decalcification, bone resorption, fibrosis of bone and marrow, cysts, numerous marrow giant cells.
12 . .	M	28	10 ¹¹ (²⁰) 15 ⁷ (⁹)	245	Agglutination, red material around eyes; ⁶ muscular weakness and hypotonia, ⁶ slightly bowing of forelimbs and knobbing at wrists ⁶	++ Moth-eaten appearance at epiphyses; pathologic fracture; rarefaction of medullary and cortical bone; slipped epiphysis	+++ Decalcification; bone resorption; fibrosis of bone and marrow, cysts, osteous tissue.
B . . .	F	7	40 ⁷ (⁷)	160	Bowing of forelimbs and knobbing of wrists; ⁶ muscular weakness and hypotonia; ⁶ found dead ¹⁷	+ Moth-eaten appearance at epiphyses	+++ Decalcification, necrotic areas in marrow; circumscribed area of fibrous tissue and giant cells in medullary cavity, cysts, fibrosis of bone and marrow; in region of epiphyseal cartilage, large area of fibrous tissue and giant cells.

		F	12	15 ⁽¹⁰⁾	90	Firm agglutination of both eyes, ¹¹ muscular weakness and hypotonia, ¹¹ found dead and almost completely eaten by litter mate ¹²	+ Moth-eaten appearance of epiphyses; slipped epiphyses	No sections.
22 . .		F						
23 . .		F	276	15 ⁽¹³⁾ 20 ⁽¹⁶⁾	515	Nasal hemorrhage, ³ suggestive knobbing of wrists and bowing of forelimbs; ¹⁶ muscular weakness and hypotonia; ¹⁹ definite knobbing and bowing; ²⁹ bowing very great, otherwise condition good; ³⁶ treatment discontinued to note changes in deformities on diet alone; ⁴⁰ deformities gradually disappeared and finally could not be detected except for a very slight knobbing of right wrist; condition of animal was excellent up to end of experiment; killed ²⁷⁶	++++ Rarefaction; series of films show progressive destruction of bone and final film shows marked healing with persistence of slight deformity of right wrist, left radius and ulna and right tibia and fibula; suggestion of kidney outline	- Except for evidence of healed fractures and overgrowth of bone, histologic appearance was normal.
28 . .		F	15	15 ⁽¹³⁾	165	Bowing of forelimbs; ¹¹ agglutination of both eyes; ¹³ muscular weakness and hypotonia; ¹³ found dead ¹⁵	++++ Rarefaction; moth-eaten appearance of epiphyses; bone destruction; suggestion of kidney outline	No sections.

Control animals grew normally, remained in excellent condition and showed normal bones roentgenologically and histologically.

* The numerals used in this column as exponents and without parenthesis represent the number of injections of the specified dose, and the numbers within parentheses represent the number of days over which these injections were spread.

† The numerals in this column represent the day of the experimental period when the observation was made.

‡ One to four plus signs are used to give a relative idea of the extent of the lesion.

The soft tissues were examined grossly and some of these were prepared for microscopic study. All of the long bones were dissected out, fixed in formalin and decalcified with 5 per cent nitric acid. Tissues for microscopic examination were embedded in paraffin and stained with hematoxylin and eosin. Mallory's connective tissue and van Gieson's stains were also used.

Results. A total of 32 rats were given parathormone in the course of these experiments with very uniform results. The protocols of several representative animals are given in tabular form to illustrate the variations observed. (Table 2.)

The most outstanding gross abnormalities were bowing of the forelimbs and muscular weakness. The time of the first detectable evidence of bowing varied from 6 to 20 days, with 12 and 15 days as an average for the production of definite deformity. The extent of this is illustrated. (Fig. 1.) A loss of muscle tone was apparent on handling the animals. Muscular weakness was also revealed by their slow limping movements and their inability to climb up the sides of cages.



FIG. 1.—Rat 21. Bowing of legs typical for rats receiving parathormone. Animal received 15 units of parathormone daily for 14 days and 15 drops of viosterol daily for 17 days. This photograph made on 19th day of experiment.

Agglutination of the eyes was seen not infrequently. The agglutinating material resembled dried blood. Blood-tinged and soft feces were noted occasionally and in 1 animal, Rat 23 (Table 2), nasal hemorrhage occurred after the third day.

Roentgenologic examinations revealed rarefaction in the bones of all rats that had received parathormone for a period longer than 3 days. This gave a mottled appearance in most cases and involved

first the ends of the long bones, later the shafts. (Figs. 2, 3, 4). The responsibility for these changes was more definitely fixed upon parathormone, and the diet was ruled out as a factor, by keeping all conditions the same after the changes appeared and discontinuing the injections. Rat 23 is typical of what then happened. The bowing disappeared and the only gross evidence of deformity was a knobbing of the right wrist which could be detected only by careful examination. The roentgenograms then showed no rarefaction or bone destruction (Fig. 5), but still some bowing of the left radius and ulna and of the right tibia and fibula, and an unevenness throughout their length of the right radius and ulna. The restitution appeared otherwise to be complete. I was able occasionally to detect a slipped epiphysis in the roentgenograms. In 1 animal there was also a slight scoliosis.

The roentgenograms of these animals do not reveal any definite intensification of shadows of the kidneys, although there is a suggestion of kidney outline in some cases. This feature will receive further comment in a subsequent paper upon the effects of the simultaneous administration of parathormone and irradiated ergosterol.

Histologically the long bones of the extremities of the parathormone-treated animals show decalcification, bone resorption, replacement of bone and marrow by fibrous connective tissue and cyst formation. These are constant findings. Giant cells resembling osteoclasts are present in large numbers and in close association with fibrous connective tissue. Giant cells are inconstantly observed in circumscribed areas of fibrous connective tissue, in the marrow cavity as well as in close proximity to bone. In some instances they appear in large number in masses of fibrous connective tissue suggesting the picture of the so-called giant cell tumor. Osteoid tissue is quite abundant in many of these skeletons and with the fibrous connective tissue almost obliterates the medullary cavity. Pathologic fractures are also numerous. The types of change observed are illustrated. (Figs. 6 to 11.) The microscopic studies of the soft tissues have not been completed, but those of the kidneys reveal metastatic calcium in the tubules and to a less extent in the interstitial tissue; not in the glomeruli.

Discussion. It was Collip's opinion, in 1926, that the rat was immune to parathyroid extracts, and this opinion has prevailed until recently. That this is not the case is evident both from my experiments and the experiments of Waltner (from which he concluded that parathormone injections wash calcium out of the bones but do not produce rickets), the experiments of Bauer, Aub and Albright (showing some bone changes after parathormone administration) and those of Rose and Stucky³⁰ (in which successive injections of parathormone produced significant increases in blood calcium).

Under the conditions of my experiments there invariably resulted

osteoporosis, bone resorption, replacement of bone and marrow by fibrous connective tissue and cyst formation. New bone (osteoid tissue) occurred with great frequency. All of this is characteristic histologically of osteitis fibrosa osteoplastica, as observed clinically. The roentgenograms and gross findings of the animal experiments are equally those of osteitis fibrosa. These results with the rat correspond to those with puppies to be reported later and to the lesions produced in guinea pigs and in dogs by Jaffe, Bodansky and Blair.^{22,23}

The bones of the rats treated with parathormone by Bauer, Aub and Albright were denser and shorter in roentgenograms, and when they were split and examined grossly appeared to contain an increased number of trabeculae. These observations are not in harmony with those I have made, but an explanation of the discrepancies is to be found, perhaps, in a difference in diet and a different dosage of parathormone. Bauer and his associates gave more calcium than my rats received, whereas their dose of parathormone was only about one-half as great as the dose I used. Under such circumstances new bone formation may keep pace with or exceed bone destruction and the newly formed osteoid tissue, which appears abundantly in many of my sections (Figs. 9 and 10), may become more or less calcified. An increase in bone density was observable in some of my experiments on the dog.²⁵

Summary. White rats, aged from 6 to 12 weeks, were injected daily for periods of from 10 to 43 days with parathormone in doses of from 10 to 20 units. A Steenbock normal rat diet was given. Uninjected litter mates as controls remained well, whereas the injected animals developed, without exception, muscular weakness, hypotonia and skeletal lesions characteristic of osteitis fibrosa osteoplastica (von Recklinghausen), namely, a lacunar resorption of bone with softening and deformity, bending and multiple fracture. The cortex and marrow of these bones were largely replaced by fibrous connective tissue containing numerous giant cells, and new bone osteoid tissue was also in evidence in numerous cases.

Conclusion. Chronic hyperparathyroidism produced in rats by repeated injections of parathormone leads to bone changes which justify a diagnosis of osteitis fibrosa. These experiments support the conclusion that the cause of clinical osteitis fibrosa osteoplastica (von Recklinghausen) is an excess of the parathyroid hormone.

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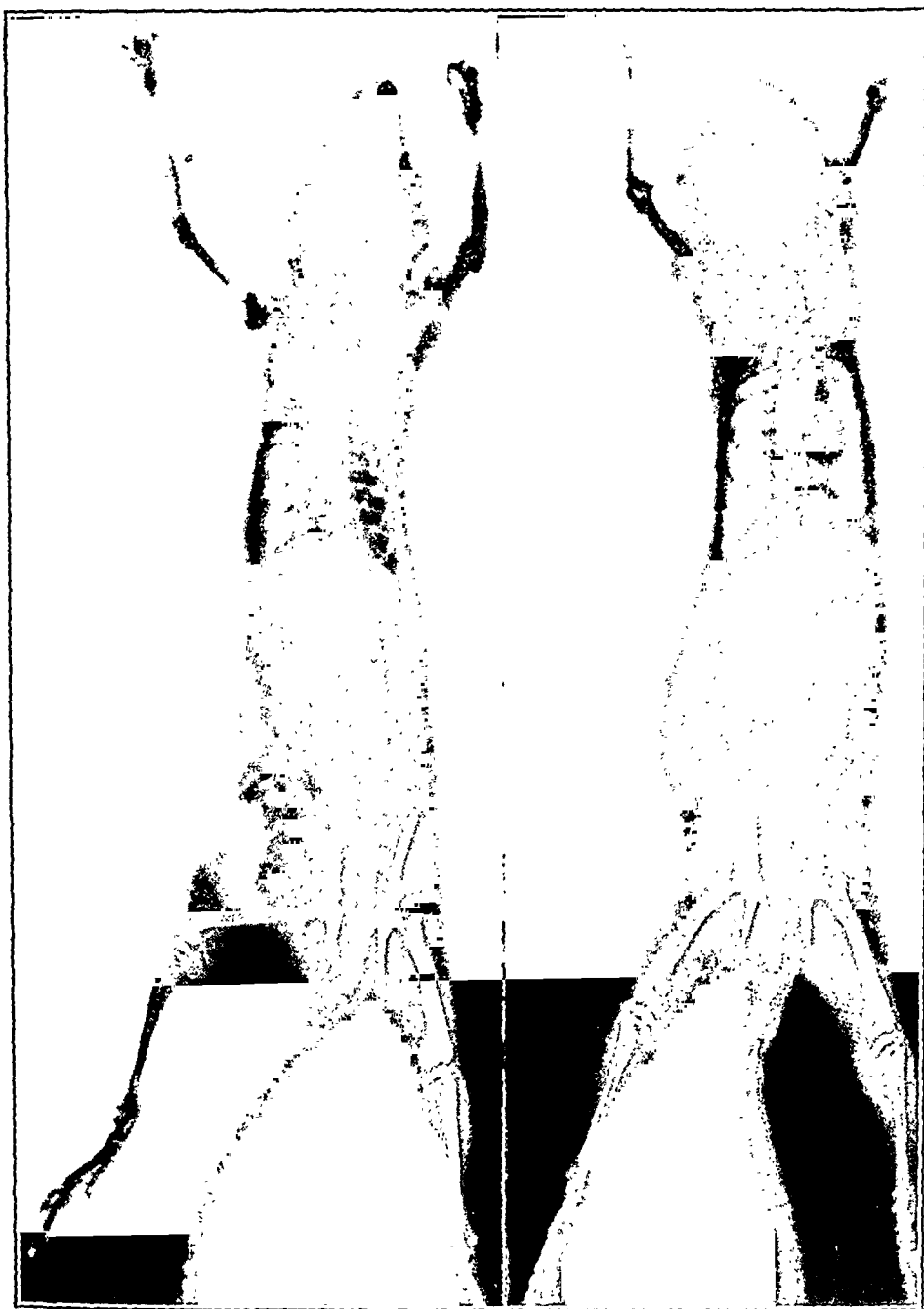


FIG. 2

FIG. 3

FIG. 2.—*Rat 23*. Bone destruction, especially at upper end of each tibia; pathologic fracture and cyst of head of humerus. Roentgenogram made on 26th day of experiment. Animal received 15 units of parathormone for 16 days and 20 units a day for last 4 days.

FIG. 3.—*Rat 23*. Roentgenogram (7 days after that of Fig. 2) shows destructive process further advanced as a result of continued treatment. Dosage of parathormone 20 units daily.

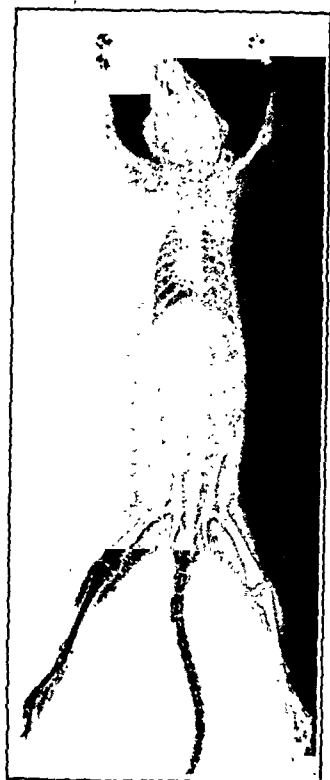


FIG. 4



FIG. 5

FIG. 4.—*Rat 23*. Destructive process 14 days later than that of Fig. 2. Treatment was discontinued after this roentgenogram was made, animal at this time had same gross appearance as shown in Fig. 1. Dosage of parathormone 20 units daily.

FIG. 5.—*Rat 23*. Upper and lower limbs of animal by roentgenogram 8 months after treatment was discontinued, diet and other conditions remaining the same. Grossly the bowing had entirely disappeared. Except for slight curvature of some bones and exostoses of one foreleg, appearance of *Rat 23* by roentgenogram at this stage was no different from that of its control litter mate as shown on same film.



FIG. 6.—Rat 8. Appearance of bone and marrow in shaft of a control animal. ($\times 60$)



FIG. 7.—Rat B. Animal died on 7th day of experiment from overdosage of parathormone. Forty units of parathormone daily for 4 of the 7 days on experiment. Resorption of cortical bone and marrow fibrosis. Small cysts can be seen in the lymphoid marrow. ($\times 30$)



FIG. 8.—Rat A. (Parathormone and viosterol). Lacunar resorption of cortical bone and marrow fibrosis. ($\times 20$) Typical picture for rats receiving parathormone. Animal died on 10th day of experiment; received 20 units of parathormone daily for 8 days and 15 drops of viosterol daily for same period.

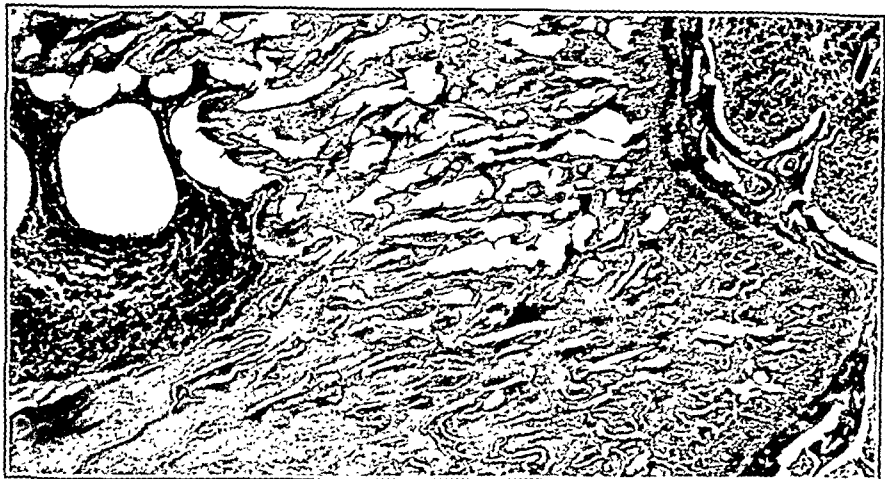


FIG. 9.—*Rat 2*. Animal killed on 42d day of experiment. Ten units of parathormone daily for 7 days, 20 units for 3 days and 15 units for 23 days. Normal appearing epiphyseal cartilage, proliferation of osteoid tissue, filling in of spaces by fibrous connective tissue and cysts in lymphoid marrow. ($\times 55$)

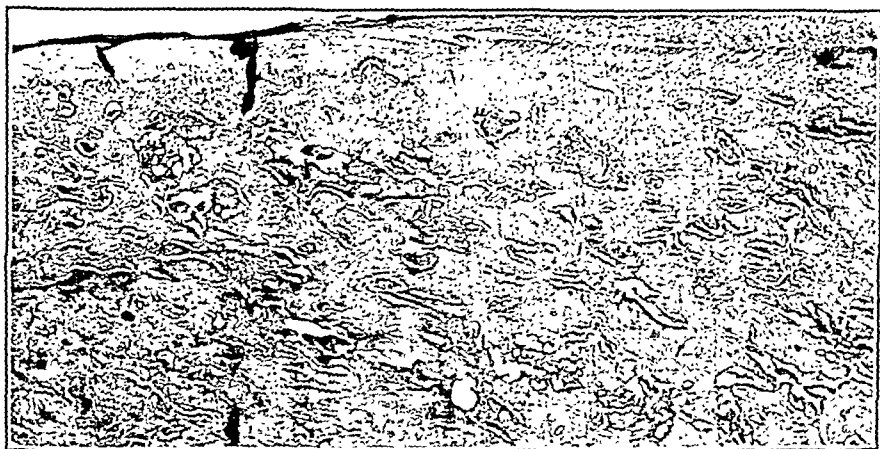


FIG. 10.—*Rat 1*. Animal killed on 42d day of experiment. Ten units of parathormone daily for 33 days. Abundance of osteoid tissue in shaft of long bone with numerous spaces filled by fibrous connective tissue. ($\times 30$)



FIG. 11.—*Rat B*. Fibrous tissue, fibrous marrow and some osteoid tissue in region of epiphyseal cartilage. ($\times 140$) (Fig. 7, *Rat B*)

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EXPERIMENTAL CHRONIC HYPERPARATHYROIDISM.

III. OSTETIS FIBROSA PRODUCED IN PUPPIES.

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THE production of a chronic state of hyperparathyroidism in experiments on man and rats has been reported and the more important literature bearing on spontaneous and experimental hyperparathyroidism is reviewed in the previous papers of this series. The present communication deals with the effects of repeated injections of parathormone in the dog.

Methods. Puppies were used because of the probability that young bones would show more striking changes from a decalcifying procedure. Their average age was about 8 weeks. Mineral balance studies were contemplated† and for this reason a synthetic diet was given to the first group of

* The expenses of this research were met from the John D. Hertz Fund.

† It proved to be impractical to conduct metabolic observations on these small animals. The repeated collection of blood was difficult to make and of questionable influence on the course of the disease; quantitative collection of urine and feces was impossible. For this reason this phase of the problem was studied with human subjects, as has been previously reported.

TABLE 1.

Dog No. and sex.	Days on experi- ment.	Parathormone administration.		Gross observations. [†]	Roentgenologic observations.	Microscopic observations.
		Dose in units.*	Total units.			
29 (Male)	62	5 ¹¹ 10 ¹¹ 15 ¹³ 20 ¹⁸	720	Bowing of forelimbs; shoulders turn outward; hind legs turn outward at hip; waddling gait; muscular weakness; ³ muscular weakness increased; sits down to eat, drink and play; ⁴⁵ watery blood-tinged stools; ⁴⁶ in jump of 18 inches from cage to floor foreleg was injured upon his animal could not place weight upon his forefoot for about 3 days; moving pictures made to show gait; ⁴⁷ skin eruption; ⁴⁸ animal quite playful and gained weight through experiment; killed; ⁴⁹ autopsy: fracture upper right humerus; purplish-red color each end both humerus and tibia; fibula very flexible; split humerus shows circumscribed brownish area corresponding to area of decreased density on Roentgen ray film; cortex thick and dense; cystic cavity at upper end right ulna 20 mm. to 3 mm; both ulnae curved.	Right upper ulna: 3 spots of decreased density 3 mm. wide, uppermost spot 10 mm. long; a third 6 mm. long; outline is quite definite and there are undoubtedly cysts; ulnae curved; left humerus: rarefaction; no evidence of cortex in region of shaft, distorted trabeculation, pathologic fracture; right humerus: distorted trabeculation at upper end, circumscribed area with finely mottled appearance; pathologic fracture; rarefaction and moth-eaten appearance of radii; femur shows increased and distorted trabeculation and cysts; fibula irregular and uneven; rarefaction of pelvis.	Upper ulna: fibrous tissue fills enlarged cortical canals, and some appears to be undergoing ossification; bone resorption; bone and marrow fibrosa; cysts; hemorrhagic into marrow spaces.
32 (Female)	..	5 ¹⁰ 10 ¹⁰⁽¹¹⁾ 15 ¹²⁽¹³⁾ 20 ¹¹	950	Muscular weakness; slight knobbing of wrists; ⁴⁴ very weak but quite playful; ⁴⁸ clouding of one cornea giving eye slate-blue appearance, cleared up after 1 week; animal stronger and more active at time of killing; ⁴⁴ condition of animal was good throughout experiment; autopsy revealed nothing of significance	Very slight rarefaction; multiple small faintly visible cysts, especially numerous in pelvis; increased trabeculation in long bones; thinning of cortex; irregular inner margin of cortex; healed pathologic fractures	Pathologic fractures; necrotic areas in bone marrow; numerous large marrow cells, not same as giant cells, resembling osteoclasts; vascularized callus; mild bone and marrow fibrosis; numerous giant cells.
51 (Male)	9	2 ⁴ 5 ⁵	33	Shows signs of failing; ⁴ very weak; ³ found dead; ³ autopsy showed death most likely due to pneumonia.	Suggestion of cysts in metatarsal and phalangeal bones; otherwise dissected bones appear normal by Roentgen ray.	Slight bone resorption; dense vascular marrow; tendency to marrow-fibrosis; hemorrhage into marrow spaces; enlargement of cortical canals; some vessels in cortex show definite thromboisis; a cystic space in one of the long bones is filled with fibrin and another contains an organizing blood clot.

33 (Male)	59	2 ¹¹ 5 ⁷ 15 ¹³ 20 ¹⁶	575	Bowing of front legs; left hind leg turns outward at hip; genu valgum; ³⁸ striking muscular weakness, especially in hind legs; deformity of left foreleg; ⁴⁴ moving picture made; ³⁷ tenderness in region of left shoulder; yelps when lifted by placing hands under arms; ³³ found dead; ⁴⁹ autopsy: split humerus shows brownish area 50 mm. x 6 mm. which corresponds in size and position to area of decreased density on Roentgen ray film; marrow hemorrhage discernible; numerous brown circumscribed areas in several bones which correspond to areas of decreased density on Roentgen ray films these are undoubtedly cysts; cortex appears quite thin and deep red color; most likely red marrow and blood shows through cortex; pathologic fracture of ulna; lungs edematous and abundant frothy material in trachea; death probably due to pneumonia; fibula flexible.	Pathologic fracture and epiphyseal separation of humerus; shows moderate rarefaction, thinning of cortex and cysts.	Bone resorption; marrow fibrosis; giant cells; cortical bone of femur almost completely destroyed; few cysts.
45 (Female)	65	5 ¹¹ 10 ¹¹ 15 ¹³ 20 ¹³	770	Watery, blood-tinged stools; ²⁰ tremors of entire body; ²² marked curvature of left leg with convexity on medial aspect; appetite poor; marked muscular weakness and hypotonia; treatment suspended for 3 days; ⁴⁶ treatment resumed, cats well, still very weak; cannot stand up to eat or to defecate; plays with other animals by crawling on abdomen; ⁴⁸ stronger and now walks a little; ³⁶ unable to stand; moving picture made; ³⁷ killed; ⁴⁸ autopsy: widened epiphyseal cartilage; marrow hemorrhage; small dark brown circumscribed areas in end of ulnae and radii and in left femur; bones bleed at ends when pressed gently with fingers; fibulae and pelvis very flexible.	Fibula curved and irregular widened epiphysis; rarefaction; left ulna shorter and wider than right; pathologic fracture; thinned cortex; epiphyseal separation; bowing; left radius shorter and narrower than right; ends of bones have moth-eaten and mottled appearance; iliac crest irregular and rarefied; cyst in ilium; fracture of pelvis anterior to acetabulum	Bone resorption; fibrosis of bone and marrow; giant cells; marrow hemorrhage; overgrowth of cartilage; isolated patch of cartilage undergoing fibrosis.

* The numerals in this column used as exponents and without parentheses represent the number of injections of the specified dose; and the numerals within parentheses represent the number of days over which these injections were spread.

† The numerals in this column represent the day of the experimental period when the observation was made.

these animals. It was composed of casein, 37.8; sucrose, 34.9; lard, 17.0; butter fat, 7.0; bone ash, 2.3 and a salt mixture, 1.2 gm. The salt mixture consisted of sodium chlorid, 10; calcium lactate, 4; magnesium, 4; ferric citrate, 1.0 gm.; iodine as potassium iodid, a few drops and vitamin B in Harris' yeast vitamin powder. This diet is Cowgill's² improvement upon Karr's diet for metabolism experiments with dogs. The animals treated with parathormone did so poorly on this regimen that it was soon discontinued. Swift's Silver Fur Kennel ration was then used for a short time and finally a supplemented meat diet consisting of ground lean meat, bread, orange juice and cod-liver oil.

With few exceptions all animals were photographed before the experiment started and at intervals during the experiment. Roentgenograms were made before and at intervals during the experiments. Roentgenograms of the dissected bones were obtained after the death or killing of the animals. The soft parts were examined grossly and some of them kept for future microscopic study. The long bones were split longitudinally and examined grossly. The split bone was fixed in formalin, decalcified in 5 per cent nitric acid, mounted in paraffin and stained with hematoxylin and eosin. In some instances Mallory's connective tissue and van Gieson's stains were used.

Parathormone was administered subcutaneously in doses ranging from 2 to 20 units daily. In order to keep the animals alive for long periods it was found to be necessary to begin with small doses and increase gradually. The average duration of the experiments was about 35 days, although some animals lived for only a few days and some of the experiments were continued for several months. Many animals were lost from over-dosage and other causes before correct conditions were established. A chronic state of hyperparathyroidism which was long enough in duration for bone pathology to develop was the objective. The diet, the dosage of parathormone and the environment all proved to be important factors for success. The supplemented meat diet proved best. Warm, dry, clean and well ventilated quarters were found to be indispensable. The dosage of parathormone would depend upon the age of the animal and its condition. The younger animals tolerated large doses badly. In every case very small doses were used at first and the amount gradually increased. A control animal of the same age, usually a litter mate, was given the same diet and maintained in the same cage with each experimental animal.

Results. A total of 35 puppies were given parathormone in the course of these experiments. Abstracts of the protocols of a few experiments selected to cover the range of observations are given in tabular form. (Table 1.) The details of earlier studies were reported last year as a dissertation for the doctorate in medicine.

It was of special interest that 5 puppies that had been treated with parathormone for varying periods developed tonic and clonic spasms when the drug was discontinued. This tetany had the earmarks of parathyroid insufficiency. It caused the death of all 5. The serum in 1 of these was found to contain 10 mg. of calcium for each 100 cc. It was not examined in the other animals.

The abnormalities noted in all of these experiments were strikingly similar. Muscular weakness, hypotonia and bone deformities were invariable. Action pictures demonstrate muscular weakness by the limping gait, inability to jump and climb and frequency of resting. Gross observations revealed lateral bowing of the fore-



FIG. 1.—Dog 6. Bowing of forelimbs after parathormone administration. Animal received a total of 46 units of parathormone in doses of from 2 to 8 units a day, and during first 7 days of experiment a total of 24 drops of viosterol in doses of from 3 to 5 drops a day. Medication was entirely discontinued on the 15th day of experiment and this photograph taken on the 16th day.

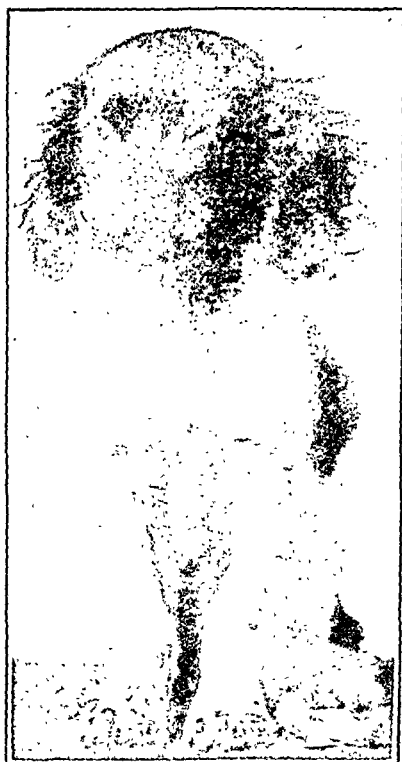


FIG. 2.—Dog 2. Knobbing of wrists following parathormone administration. Sixteenth day of experiment. Animal started on 12 units daily and reduced on 3d day to 8 units daily. Injections were discontinued on 9th day because of failing condition of animal.

limbs and knobbing of the wrists of the majority of these animals (Figs. 1, 2 and 3). The roentgenograms show rarefaction, moth-eaten appearing areas, increased and distorted trabeculation and cysts of the long bones (Figs. 4 and 5). In some cases the pelvis was likewise involved. In some instances cysts were large enough to be plainly visible to the unaided eye when the long bones were split (Fig. 6). The most outstanding histologic changes were osteoporosis, resorption of both cortical and trabecular bone, enlargement of Haversian and communicating canals, the filling of



FIG. 3.—Dog 45. Deformity of forelimbs following parathormone administration. Photographed on 41st day of experiment. Started on 5 units daily and gradually increased to 20 units.

these spaces by fibrous connective tissue, proliferation of osteoid tissue and cyst formation. Giant cells with numerous small, round nuclei appeared in large numbers, associated with fibrous connective tissue as well as in close proximity to bone which was undergoing resorption (Fig. 8).

Only in Dog 45 was there any apparent disturbance in growth of the epiphyseal cartilage. In this animal a marked overgrowth of cartilage cells suggested rickets, but even here there was a marked associated replacement of bone and marrow by fibrous connective tissue, as well as bone resorption and proliferation of osteoid tissue.

An occasional but infrequent observation was a slate-blue color-

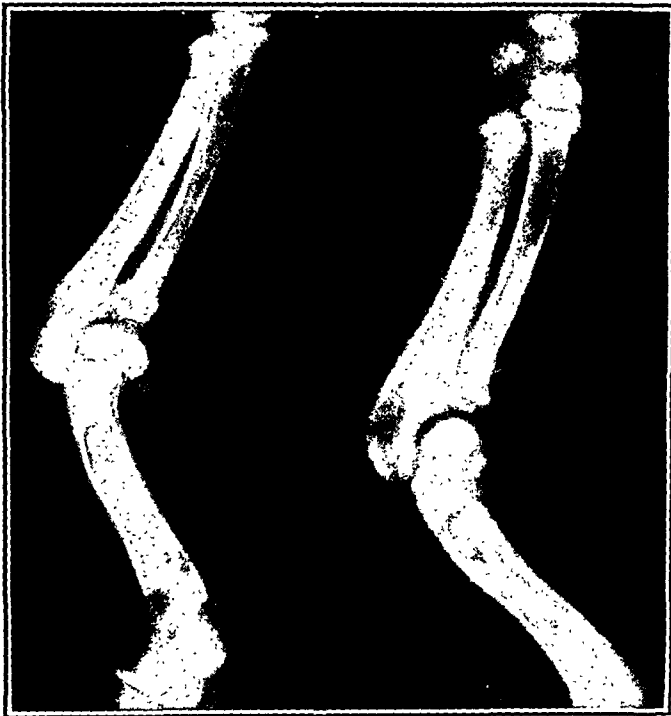


FIG. 4.—Dog 6. Cysts in humeri.

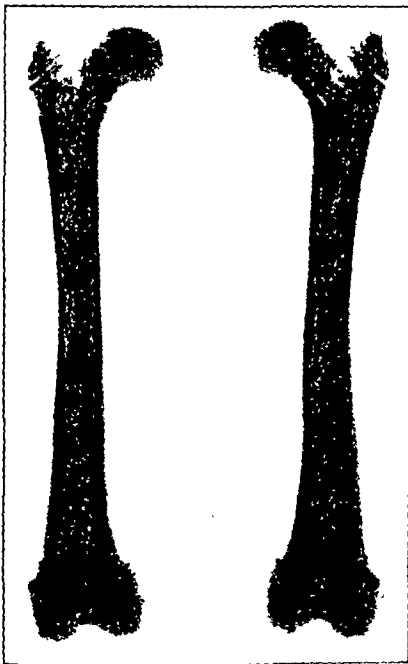


FIG. 5.

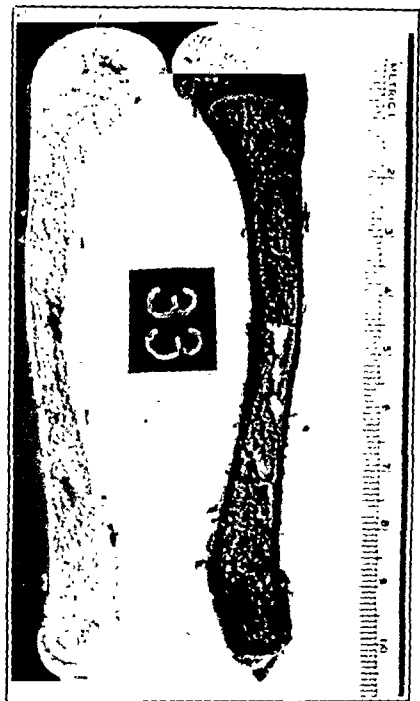


FIG. 6.

FIG. 5.—Dog 29. Left and right femur. Multiple cysts. Illustrations in Fig. 5 of Dog 29 were made at the termination of the experiment on the 62d day. Animal had received from 5 to 20 units of parathormone daily for a total of 720 units.

FIG. 6.—Dog 33. Two halves of right femur showing gross appearance of cysts. Five to 20 units of parathormone daily for a total of 575 units. Animal died on 59th day of experiment, at which time photographs were made.

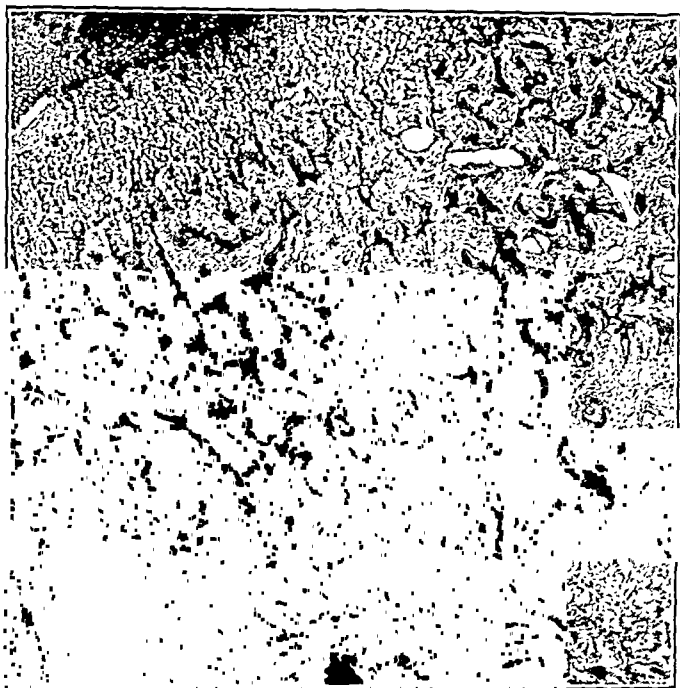


FIG. 7.—Dog 45. Animal killed on 65th day of experiment. Five to 20 units of parathormone daily, total 770 units. Lower end of femur. Principally fibrosis and osteoid tissue. ($\times 30$.)



FIG. 8.—Dog 42. Animal received 5 to 20 units of parathormone daily, total 777 units; and 40, later 20, drops of viosterol daily, total 1340 drops. Killed on 67th day of experiment for histologic study of bones. Three multinucleated giant cells and marrow fibrosis. ($\times 250$.)

tion which completely obliterated the transparent appearance of the cornea.

Discussion. With suitably nourished and well-cared-for puppies and proper precautions regarding dosage, it is thus possible to reproduce experimentally, by repeated injections of parathormone, a clinical picture that closely resembles the osteitis fibrosa osteoplastica described in man by von Recklinghausen. Similar results have been obtained with the rat⁴ and by Bodansky and Jaffe¹ in the guinea pig and dog. A wide variety of symptoms and abnormalities had been noted in the human disease. In the experiments described on rats, dogs and man the repeated injection of parathormone has caused practically every peculiarity that has been noted clinically. Not all of these changes have been observed in any one animal any more than all have been observed clinically in any single case, but those which occur often enough in the spontaneous diseases of man to be of diagnostic importance have been reproduced with great regularity by these experiments.

The confusion of nomenclature in connection with diseases of the bone is particularly apparent in the literature of hyperparathyroidism, and although it was expected that a bone disease would result from such repeated injections of parathormone it could not be foretold whether this would be osteitis fibrosa, osteomalacia or rickets. Erdheim postulated that the enlargement of the parathyroids, seen so often in association with osteomalacia, represented an inadequate attempt at compensation and some clinicians have credited him with the same view for osteitis fibrosa and have used the terms osteomalacia and osteitis fibrosa interchangeably. From the results of these experiments, and others to be reported, in which animals receiving parathormone were simultaneously treated with viosterol, it is evident that the two diseases are distinct and that hyperfunction of the parathyroid glands, while secondary in the case of osteomalacia or rickets, is a primary factor in the pathogenesis of osteitis fibrosa. The relationship of these conditions will be discussed more fully in a subsequent report.

Summary. The experimental production in puppies of a state of chronic hyperparathyroidism is reported and descriptions are given of the gross, roentgenologic and microscopic abnormalities resulting therefrom. This experimental disease, produced with repeated injections of parathormone, is characterized by skeletal lesions and other abnormalities which correspond closely to those observed in clinical cases of osteitis fibrosa osteoplastica (von Recklinghausen).

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EXPERIMENTAL CHRONIC HYPERPARATHYROIDISM.

IV. EFFECTS OF ADMINISTRATION OF IRRADIATED ERGOSTEROL.

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THE production of chronic experimental hyperparathyroidism in man, rats and dogs has been discussed in three previous papers.^{10,11,12} The skeletal lesions resulting from repeated injections of parathormone are those observed in a disease first described by von Recklinghausen and named by him osteitis fibrosa osteoplastica. The influence of irradiated ergosterol on the course of this experimental disease is the subject of the present communication.

A relationship between the parathyroid glands and vitamin D has been suggested by the observations of a number of investigators. Nonidez and Goodale,¹⁶ and Higgins and Sheard⁸ noted hyperplasia of the parathyroids in fowls deprived of vitamin D. Hess, Lewis and Rivkin⁷ found that irradiated ergosterol no longer raised the level of serum calcium in a parathyroidectomized monkey although the same animal had, previous to operation, responded by a rise to the normal from a serum calcium level previously lowered by a diet deficient in calcium. Similar observations on dogs led them to the conclusion that vitamin D would stimulate parathyroid activity. Prevailing views as to the mechanism of this action are conflicting. Morgan and Garrison¹⁵ agree with Hess that parathyroid activity is more pronounced in the presence of vitamin D, but differ from him by denying that any more hormone is produced. In other words, the action of the vitamin according to them is upon the hormone rather than the glands. Also Jones, Rapoport and Hodes¹⁴ have produced hypercalcemia in parathyroidectomized dogs when large doses of irradiated ergosterol were used and have found that a pre-operative administration of irradiated ergosterol prolongs life, and either prevents or delays the onset of tetany in thyroparathyroidectomized dogs. They are thus agreed with Morgan and Harrison that the action of vitamin D is not upon the glands and regard its effects as supplementary to those of the hormone.

From incompletely controlled observations in a clinical case of osteitis fibrosa with parathyroid gland tumor, the impression was gained that cod-liver oil (vitamin D) was clinically beneficial. Wilder²⁰ pointed out that an antagonism was suggested by this observation, and Compere³ and Quick and Hunsberger¹⁷ have since

* The expenses of this research were met from the John D. Hertz Fund.

reported clinical experience which seemed to substantiate this hypothesis of antagonism. However, the interpretation placed upon the experiments of Nonidez and Goodale, and of Higgins and Sheard, namely, that the action of the parathyroids and vitamin D is supplementary, is quite untenable if this is true, because, as Wilder stated, "if irradiated ergosterol supplements the parathyroids its exhibition should aggravate, certainly not benefit, conditions attributable to overfunctioning of the parathyroid glands."

It was for the purpose of obtaining more definite experimental evidence in this problem that irradiated ergosterol was given to animals receiving parathormone. The results obtained have convinced me of the essential difference between either osteomalacia or rickets and osteitis fibrosa. The osteitis produced by chronic injections of parathormone^{9,10,11} was actually aggravated by the simultaneous administration of irradiated ergosterol and no antagonism whatsoever could be demonstrated.

Methods. The study covers experiments with rats, dogs and human subjects. Metabolic investigations formed the most important feature of the observations on man. The methods and results of these have been reported by Johnson and Wilder.¹² In the work with rats and dogs the same methods were used as were reported^{10,11} for experiments with parathormone alone, except that irradiated ergosterol (viosterol) was administered by mouth. Litter mates of the animals which received parathormone alone served for this purpose, the experiments running simultaneously. The same dosage of parathormone was used in both groups of animals. The rats received 10 to 20 units of parathormone daily, and 10 to 15 drops of viosterol.* In the case of Rat 5, 15 to 60 drops were given, and Rat 7, received 15 to 30 drops (Table 1). The puppies had from 2 to 20 units of parathormone daily and from 3 to 40 drops of viosterol. The latter was mixed with the food for the rats and in the case of the puppies was dropped directly into the back part of the mouth. Its introduction always preceded the parathormone injections by several days. Other litter mates on identical diets, but no medication, served as controls.

One rat, No. 30, was carried on viosterol alone for 24 days and then upon parathormone and viosterol for 5 days (Table 1).

Results. Fifteen puppies and 20 rats received viosterol together with parathormone in this series of experiments. Illustrative protocols are presented in the accompanying tabulation. The results in the early studies with puppies suggested some protection from the irradiated ergosterol, but later experiments with puppies and rats, and the metabolic data obtained with human subjects, disprove this and clearly indicate that irradiated ergosterol not only is not antagonistic in its action but actually intensifies the effects of parathyroid hormone. The same outstanding lesions, observed by gross, roentgenologic and microscopic examinations in the parathormone experiments^{10,11} were equally and usually more prominent in animals treated with both parathormone and irradiated ergosterol. (Figs. 1 to 12.)

* A dropper furnished with the Johnson-Mead product was always used.

Among the most interesting additional observations in the parathormone viosterol experiments was a marked metastatic calcification of the kidneys. In no instance, when parathormone was



FIG. 1.—Dog 42. Bowing of fore legs after parathormone and viosterol administration of 38 days. Animal received from 5 to 20 units of parathormone daily during this period. For first 11 days of experiment 40 drops of viosterol was given each day after which dose was reduced to 20 drops daily.

given alone, could the kidney be definitely visualized by roentgenograms, although in 2 cases in rats there were faint outlines sugges-

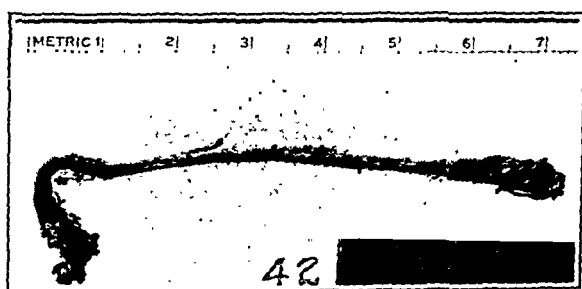


FIG. 2.—Dog 42. Flexible and fibrous right fibula after parathormone and viosterol administration. Animal killed to terminate experiment on 67th day. In 52 days 777 units of parathormone was administered in doses of from 5 to 20 units a day. 1340 drops of viosterol was given in 56 days, 40 drops a day for first 11 days and 20 drops for 45 days.

tive of such visualization. With the simultaneous administration of parathormone and viosterol the kidney of the rat was repeatedly and clearly visible in the roentgenograms. (Fig. 3.)



FIG. 3.

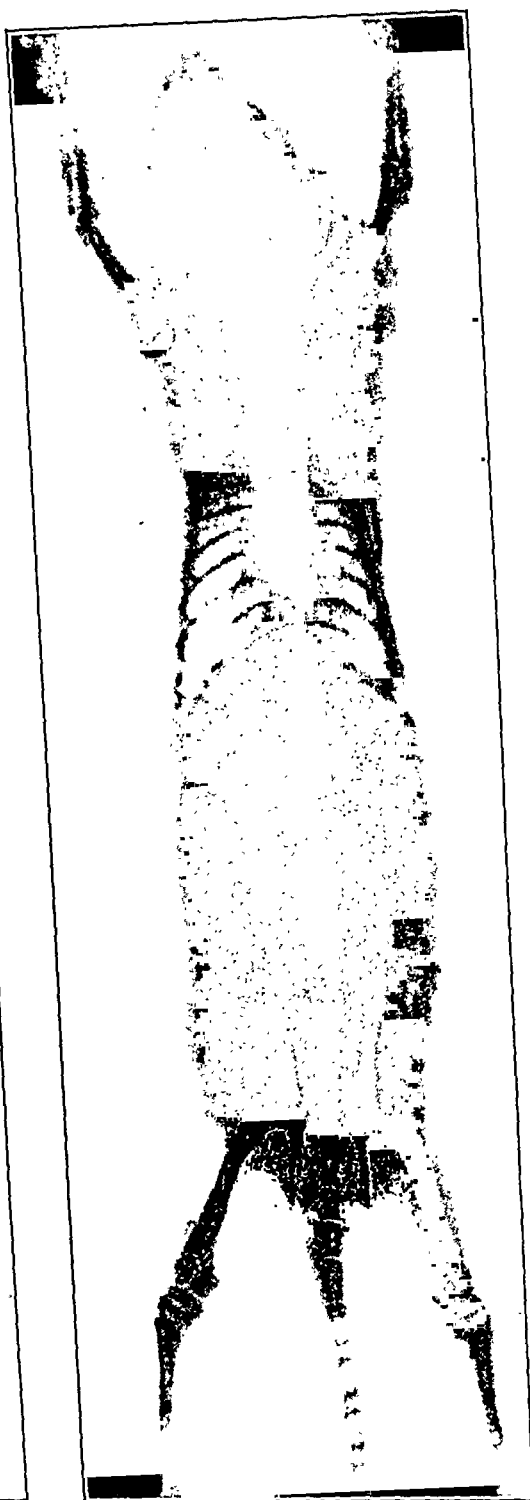


FIG. 4.

FIG. 3.—Rat 5. Rarefaction and resorption of long bones, kyphoscoliosis and calcified kidneys. Roentgenogram made at termination of experiment on 42d day. A total of 430 units of parathormone had been administered in 31 days in doses of from 10 to 20 units per day. 1240 drops of viosterol was given in 51 days in quantities of from 15 to 60 drops a day.

FIG. 4.—Rat 21. Marked bone destruction at upper end of each tibia and slipped epiphysis at head of humerus. Roentgenogram made on 26th day of experiment. A total of 210 units of parathormone in doses of 15 units a day and a total of 255 drops of viosterol at rate of 15 drops a day had been administered. Fig. 5 shows healing in same animal 7 days later.

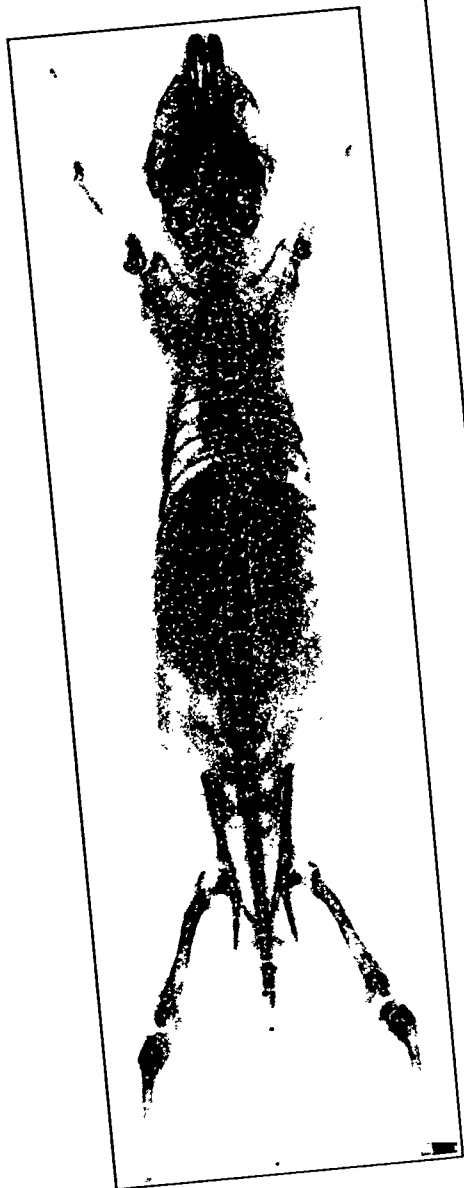


FIG. 5.



FIG. 6.

FIG. 5.—Rat 21. Healing at the upper end of each tibial after medication had been stopped for 7 days. Fig. 4 shows the condition before medication was stopped.

FIG. 6.—Rat 30. Animal used to determine whether or not viosterol alone would cause calcification of kidneys to extent of roentgenologic visualization. 15 drops of viosterol per day was given for 24 days. No evidence of bone lesions or calcification of kidneys after 8 days on viosterol. (In series with Figs. 7 and 8.)

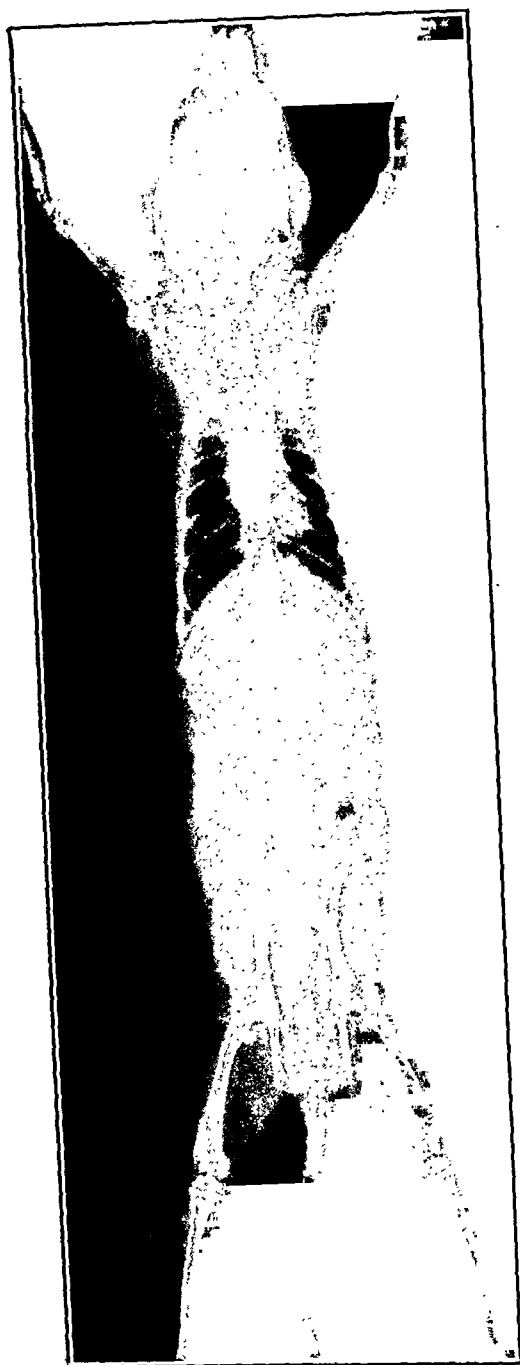


FIG. 7.

FIG. 7.—Rat 30. No evidence of bone lesions or kidney calcification after 24 days on viosterol. (Roentgenogram made 16 days after Fig. 6.)



FIG. 8.

FIG. 8.—Rat 30. Rarefaction of skeleton bone destruction and striking calcifications of the kidneys. This roentgenogram was made 7 days after that shown in Fig. 7. During the first 4 of these 7 days the animal received 15 units of parathormone daily in addition to viosterol.



FIG. 9.—Rat A. Resorption of cortical bone. ($\times 60$.) Animal died on 10th day of experiment and had received 20 units of parathormone daily for 8 days and 15 drops of viosterol a day for 8 days.

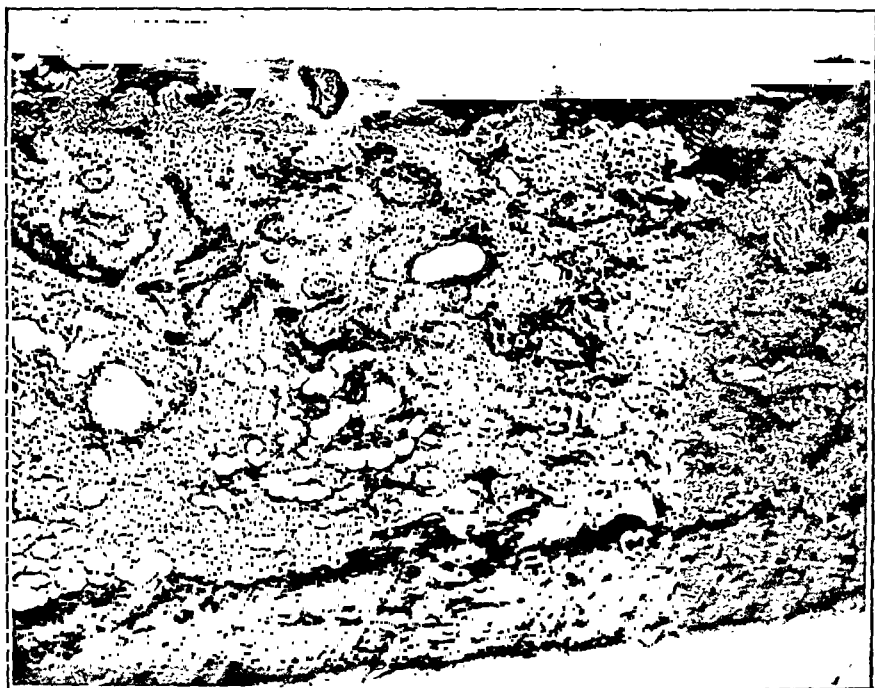


FIG. 10.—Rat A. Fibrous tissue replacement of bone and bone marrow, lacunar resorption, cysts, osteoid tissue and giant cells. ($\times 60$.) See legend of Fig. 9.

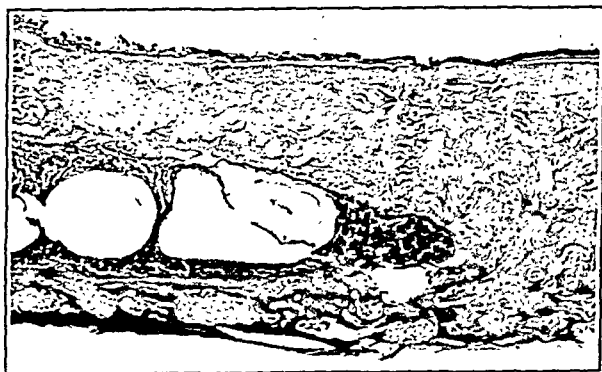


FIG. 11.—Rat 5. Fibrous tissue replacement of bone, filling in of enlarged canals of the cortex by fibrous tissue, cysts and osteoid tissue. ($\times 30$.) See legend of Fig. 3.

In order to answer the question as to whether or not irradiated ergosterol was alone responsible for this greater degree of metastatic calcification, Rat 30 was kept on this vitamin D concentrate for 24 days, before being given parathormone. At the end of that time no metastatic calcification was evident roentgenologically (Figs. 6 and 7), and on the twenty-fifth day 15 units of parathormone was injected. This dose was continued for 3 days, whereupon the previously excellent condition of the animal changed to a poor one. The dose was then decreased to 10 units for 1 day and discontinued. In roentgenograms made when this treatment was stopped the kidneys are clearly visible. (Fig. 8.) The animal died 2 days later.

The roentgenograms of Rat 21 bring out another interesting feature, namely, the rapidity of healing of the skeletal lesion. This animal had developed all of the gross deformities and roentgenographic changes of osteitis fibrosa. (Fig. 4.) With other conditions remaining the same, parathormone and viosterol were discontinued. Seven days later roentgenograms revealed a very striking amount of healing. (Fig. 5.)

The histologic examinations of the bones of both the rats and dogs in these experiments revealed extensive resorption of trabecular and cortical bone, proliferation of osteoid tissue, cyst formation, giant cells and replacement of bone and marrow by fibrous connective tissue. (Figs. 9, 10 and 11.) The kidneys showed enormous calcium deposits in the tubules and interstitial tissue but no stone formation. (Fig. 12.)

Discussion.—A comparison of the results in these experiments with those reported previously^{10,11} shows that the skeletal abnormalities were as great and usually greater when irradiated ergosterol accompanied the injections of parathormone. Also, as reported earlier,¹² the pain, muscular weakness, headaches and lassitude experienced by the human subject were worse during the period of parathormone and irradiated ergosterol than they had been during the parathormone period. The negative calcium and phosphorus balances of the parathormone period of the human experiment became greater during parathormone and irradiated ergosterol administration.¹² These observations indicate that irradiated ergosterol actually aggravates the conditions attributable to hyperparathyroidism.

Metastatic calcification has been frequently reported in conditions of parathyroid overfunction, and likewise in connection with the administration of irradiated ergosterol. The kidney in each instance has been one of the most frequent tissues affected. I have found, however, no clinical or experimental reports of renal calcification sufficiently intense to render the kidney visible by roentgenogram. In these experiments neither parathormone nor irradiated ergosterol alone produced sufficient calcification for kidney visualiza-

tion, but when the two substances were administered simultaneously the kidneys could be clearly seen. (Fig. 3.) On microscopic examination calcium was found in the tubules and to a less extent in the interstitial tissue in the parathormone as well as the parathormone irradiated ergosterol animals, but much more abundantly in the latter. (Fig. 12.) There was also considerable damage to renal parenchyma. Nephritis and nephrolithiasis, seen clinically in association with tumor of the parathyroid gland and osteitis fibrosa, may well be explained on the basis of this metastatic calcification.

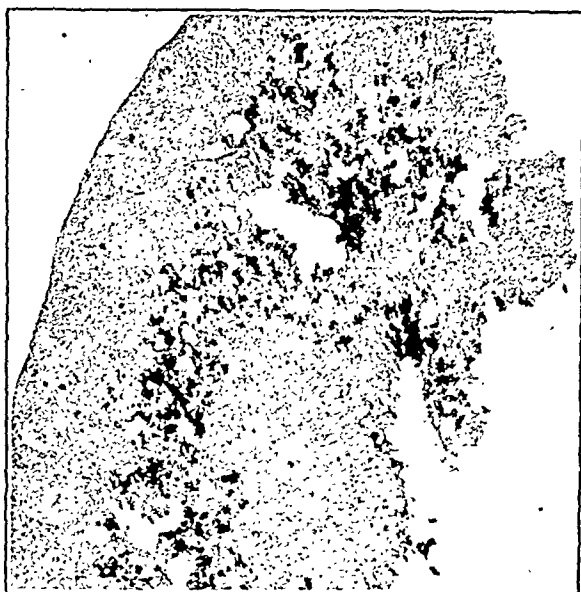


FIG. 12.—Rat 5. Calcium deposits in kidney. ($\times 12$.)

These experiments permit of the following interpretation. Vitamin D either stimulates the parathyroid glands to secrete more hormone or intensifies the activity of the hormone in circulation or supplements in its action the effect of the hormone. They certainly bring no evidence of inhibition of the glands or neutralization of the hormone, and consequently no support for the clinical treatment of states of hyperparathyroidism with cod-liver oil, ultraviolet light or irradiated ergosterol. The danger of intensifying metastatic calcification is very real, and for this, if for no other reason, treatment with vitamin D is definitely contraindicated in osteitis fibrosa.

The outcome of the study also indicates the complete etiologic dissimilarity between the osteitis fibrosa and rickets or osteomalacia. The skeletal lesions of the former are intensified by vitamin D concentrates which are so beneficial in the latter. The hypertrophy

of the parathyroids that accompanies rickets, as noted first by Erdheim, and the similar hypertrophy of these glands that occurs in fowls that are grown under amber light or are otherwise deprived of vitamin D is a phenomenon secondary to vitamin D deprivation. It may be an attempt at compensation, as originally suggested by Erdheim. That such gland produces more hormone than normal is not improbable, but that this increased hormone output is not in excess of the tissue demand is shown by the absence of lesions like those which appear when parathormone is administered to normal animals. In osteitis fibrosa we have to deal with normal demand and excessive supply of hormone, for which a primary enlargement of parathyroids is responsible. These conclusions are in harmony with the observation that in rickets and osteomalacia hypertrophy involves all of the parathyroids with more or less uniformity, whereas it is a rule in osteitis fibrosa for one or at most two glands to be enlarged as tumors with the remainder remaining normal in size and structure. The case of osteitis fibrosa studied by Hannon and his colleagues,⁶ and later operated upon by Richardson,¹⁸ is no exception to this rule. A careful surgical exploration of the neck failed to reveal either a tumor or any general hypertrophy of the parathyroids, but this only suggests that overfunction of parathyroids and excessive hormone supply may occur in the absence of anatomic abnormalities. Several analogies can be cited, particularly the healthy appearance of the islets of Langerhans in certain outstanding instances of hyperinsulinism, as reported by Allan¹ and the Finneys.⁴

Summary. An answer was sought to the question as to the relationship of osteitis fibrosa to those other skeletal diseases, especially rickets and osteomalacia, that are also associated with hypertrophy of parathyroid glands. Metabolic studies of the problem have been reported previously; the results of animal experiments are given here. Irradiated ergosterol, in a dosage of 5 to 60 drops daily, was fed to young, white rats and puppies maintained in a chronic state of hyperparathyroidism by the daily injection of parathormone. These animals were litter mates of others that developed the skeletal lesions of osteitis fibrosa when treated with parathormone alone.^{10,11} The technique of experimentation, the diets and dosage of the parathormone was the same as that previously reported.^{10,11} The outcome was the same, except that the resulting lesions typical of the skeletal abnormalities of osteitis fibrosa were, on the whole, more extensive. Metastatic calcification in the kidneys was also more marked.

Whereas vitamin D concentrates effectively protect against rickets or osteomalacia, it is evident from these experiments that they intensify the disease produced by excess of parathyroid hormone. It is, therefore, clear that rickets or osteomalacia differ essentially in pathogenesis from osteitis fibrosa. While the hypertrophy of

the parathyroids in conditions of vitamin D deficiency may be compensatory and is certainly a secondary phenomenon, the tumors of parathyroids found in association with osteitis fibrosa are of primary significance. It is recognized, however, that overfunction of parathyroids may occur in the absence of tumors or other morphologic abnormality.

The technical assistance of Mrs. Helene Wallace and of Mrs. Estellena G. Johnson in the preparation of the histologic sections in these experiments is gratefully acknowledged.

NOTE.—I desire especially to acknowledge invaluable suggestions and criticisms from Dr. Russell M. Wilder.

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IDIOSYNCRASY TO VIOSTEROL.

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It has been fairly well established by animal experimentation and clinical observation that excessive doses of irradiated ergosterol are capable of producing definite ill effects. Relatively few instances of disturbances due to small amounts are mentioned in the literature. The present study was undertaken because observation seemed to indicate that the prevalence of idiosyncrasy to viosterol is greater than hitherto reported.

About 1 year ago we encountered in our private practice several instances of mild enteric disturbances of obscure origin which occurred in infants without any apparent relationship to change of diet or parenteral infection. Observation revealed that these ill effects were prevalent among those who were receiving prophylactic doses of acterol or viosterol, 100 D. It was decided to investigate further to determine a possible relationship to the medication.

Scope of Investigation. Irradiated ergosterol in the form of viosterol, 100 D or 250 D (after the introduction of the latter) was administered to 200 infants who continued under our observation for a period of from 6 months to 1 year. Treatment was instituted at the age of 7 weeks if possible or at the time of the first visit. The initial dose was 1 drop 3 times a day for 4 days and then increased 3 drops a day every fourth day until a total of 5 drops 3 times a day was reached. This latter dosage was not increased except in cases of prematurity or florid rickets. The final dose was continued for the entire period of observation or until untoward symptoms were observed. Ill effects resulting from more than 9 drops a day are considered due to excessive dosage and not as instances of idiosyncrasy.

In those infants who showed any disturbances, the viosterol was immediately discontinued and the mother instructed to render daily telephone reports of the subsequent condition of the child. The medication was suspended for 3 or 4 weeks and then resumed in 1-drop doses 3 times a day and increased every fourth day as indicated above. The mother continued to report daily until the case was placed in the idiosyncrasy or nonidiosyncrasy group. A physical examination and change of diet was made every 4 weeks. It was considered at the onset of the study to consider only those disturbances as being due to the action of viosterol which showed the following sequence: The ill effects appeared after administration of viosterol, subsided upon its suspension and reappeared upon its resumption. No case was to be included within the idiosyncrasy group unless this repetition of symptoms occurred and recurred.

To determine whether the results were produced by irradiated ergosterol or by the oil medium, it was decided to administer the latter without viosterol. Nonirradiated maize oil, obtained through the courtesy of Mead, Johnson & Co. and stated by them to be the medium used in their product, was administered to 5 infants who had previously shown ill effects on viosterol. The dosage was equal to that of the original administration of the drug and was given for 1 week. Unfortunately we were able to obtain consent of only 5 mothers and our findings for this phase of the study are therefore inconclusive.

Previous Condition of Infants in Idiosyncrasy Group. A consideration of the previous health of the infants who reacted to the drug is important for a proper evaluation of the study. It so happened

that all but 2 were artificially fed. The health and general condition were good as attested by increasing weight and normal development along mental and physical lines. None of the infants presented any signs of rickets at the onset of treatment.

There was a previous history of vomiting in 3 infants which had been controlled prior to the institution of treatment. The administration of even 1 drop of viosterol in 2 was followed almost immediately by vomiting, but in the third infant there was no recurrence. No child was included in this group who had a previous history of diarrhea. Constipation was present in 4.

Results. Of the 200 infants studied, 15 showed untoward symptoms and form the basis of this report. There were, however, numerous other instances where ill effects appeared after 1 administration, but through the mother's refusal to continue the procedure as indicated above, they are not included. In another small percentage of cases also not included, the disturbances appeared after the drug had been given but did not reappear upon its resumption.

In the 15 cases cited, untoward results appeared almost immediately or within 1 or 2 days. These disturbances were found with doses ranging from 1 drop given only once to 3 drops 3 times a day. A few instances were noted of a continued disturbance after the drug had been stopped, confirming Hess¹ belief in its progressive action. Schmidtman,² on the basis of experimental work on cats and rabbits, also concluded recently that the drug exerts an effect on tissues even after it had been discontinued.

The ill effects in the order of their frequency were: loose bowel movements, vomiting, loss of appetite, colic and stationary or loss of weight. These symptoms usually appeared in various combinations, but only 1 infant manifested all the possible effects while 5 showed only 1 disturbance.

Diarrhea. The most frequent untoward symptom was an alteration in the character of the stools, occurring in 12 infants. The effect varied from 2 to 3 soft, normal movements to a definite diarrhea of numerous, loose, watery, yellow or green evacuations which were slimy in some instances. The condition generally subsided within a day after the drug had been discontinued, but in 2 instances a continued action necessitated a change to lactic acid or protein milk feeding. It was a fairly common occurrence for an infant with a previous obstinate constipation to pass 1 or 2 soft stools after the administration of viosterol. The dose of tolerance ranged from 1 to 9 drops, varying with each individual. In comparison to the infant who could not tolerate even 1 drop, there was the other who showed no ill effects until given 9 drops a day. In 1 child, 3 to 4 loose, yellow movements a day appeared as long as viosterol was administered. The largest number of stools noted in 1 day was 25, in a physician's child.

Vomiting. Vomiting was noted in 8 infants, occurring in all but 1 as an associated symptom. In some it followed almost immediately upon the administration of viosterol, while in others it did not appear until 2 days later. Instances of slight spilling are not considered under this heading. Suspension of the medication generally resulted in a cessation of disturbance except in 2 infants, in whom it continued for 3 and 4 days respectively. In every instance vomiting eventually subsided with the discontinuation of the drug and recurred on its resumption.

Loss of Appetite. Loss of appetite was not considered an untoward symptom unless it appeared in combination with other ill effects, because of its common occurrence during infancy. In some infants an impairment of appetite was dominant while in others it was of secondary importance. As with the other ill effects, it appeared either immediately or within a few days after the institution of treatment. One infant illustrated the rapidity with which viosterol acted at times. He received 1 drop in orange juice at 8 A.M., he refused his bottle at 9 A.M. and experienced an attack of severe colic at 12 noon. Subsequent administration always resulted in almost instantaneous loss of appetite.

Colic. Intestinal colic was present in 4 infants and always in association with other symptoms. The latter were diarrhea and vomiting in 3 infants and loss of appetite in 1. At no time did it occur in combination with constipation as reported in J. H. Hess' series with excessive dosage.³ The effects were immediate in every case with a dosage ranging from 1 to 3 drops. One infant vomited immediately after the ingestion of 1 drop of viosterol but reacted to 3 drops by a severe attack of colic, diarrhea and vomiting.

Weight. The general condition of the infants was not affected by the occurrence of untoward symptoms. There was an increase in weight in all but 3. Stationary weight was found in 2 children and was associated with loss of appetite, vomiting and 2 or 3 loose movements a day. One showed in addition an intolerance to Alpine lamp treatment as evidenced by stationary weight and loss of appetite during the entire course of treatment. Both infants gained in weight on the discontinuance of viosterol without any change in diet. Loss of weight was encountered in 1 infant who had a protracted diarrhea following administration of viosterol and which continued for weeks after the drug had been stopped. The effect on weight in these 3 infants may well be attributed to the composite action of associated symptoms and not to the direct effect of viosterol.

Rash. Two instances of rash, one erythematous and the other maculopapular, seemed to be due to administration of viosterol but are not included within the 15 cases of idiosyncrasy because of failure to reappear upon the resumption of the medication.

TABLE 1.—RÉSUMÉ OF SYMPTOMS OBTAINED IN IDIOSYNCRASY TO VIOSTEROL. (IRRADIATED ERGOSTEROL.)

Case No.	Sex.	Age.	Dose in drops.	When noted.	Stools.	Vomiting.	Loss of appetite.	Colic.	Weight.	Remarks.
1.	F.	6 mos.	1 b.i.d. on first day	Second day	Loose, yellow. 1-2 a day	Marked. Recurred with one drop every time it was given	Began on second day and continued for 6 days.	None	Stationary	
			1 t.i.d. next day	Recurred on taking viosterol			
2.	F.	3 mos.	1 t.i.d.	Same day	Large number of loose watery yellow stools (25 in one day)	Continued for 4 days. Recurred every time viosterol was given	Marked	None	Good	
3.	M.	7 wks.	1 drop	One half hour	Normal	Marked. Recurred almost immediately after every administration	Marked for entire time of viosterol administration	None	Stationary	Also had intolerance to Alpine lamp.
			3 drops	2-3 hrs.	Loose and yellow. 3-4 that day	Marked—simultaneously with diarrhoea and colic	Simultaneous with vomiting and diarrhoea		
4.	F.	2 mos.	1-2 drops a day	Same day	Loose, yellow green, 5-6 a day. Continued for week after viosterol was discontinued. Protein milk necessary	None	None	None	Lost during period of diarrhoea	
			Later could not tolerate 1 drop a day	Recurred with even 1-drop doses subse- quently					
5.	F.	3 mos.	2 t.i.d.	Same day	Loose and yellow. 5 times that day. Recurred every time it was given. Continued for 10 days	None	None	None	Good	

6.	F.	3 mos.	3 t.i.d.	Almost immediately	Loose, yellow, slimy, 4 a day. Recurred after every administration	None	Marked from onset of treatment	None	Good
7.	M.	13 wks.	2 t.i.d.	Same day	Loose and watery, 4 times that day. Continued for 24 hours after discontinuing viosterol	Marked	None	Simultaneous with diarrhea and vomiting	Good
8.	M.	4 mos.	3 t.i.d. 5 t.i.d.	Same day	Soft and formed. Continued 3-4 a day for months Loose, yellowish-green, watery and slimy	None None	None	None	Good Viosterol given for entire time.
9.	F.	3 mos.	1 drop	One hour	Normal	None	Refused feeding 1 hour later	Severe 4 hours later.	Good Recurred on second trial.
10.	M.	9 wks.	2 t.i.d.	Same day	Loose, yellow, slimy, 4-5 a day. Recurred even after 1 drop t.i.d. and continued for a few days after viosterol was discontinued	None	None	Present at times with diarrhea	Good Lost intolerance in 1 year.
11.	F.	4 mos.	2 t.i.d.	Same day	Loose, yellow, 4 that day. Recurred on two subsequent administrations	None	None	None	Good
12.	M.	3 mos.	3 t.i.d.	Same day	Loose and yellow every time	With every dose	None	None	Good
13.	F.	2 mos.	2 t.i.d.	Same day	Normal	With every dose	Impaired appetite throughout	None	Good
14.	F.	10 mos.	1 b.i.d.	Immediate	Normal	Marked. Continued for 3 days. Recurred every time	None	None	Good
15.	M.	1 mo.	1-2 t.i.d.	Immediate	Loose, watery, yellow. Recurred on 1 drop	None	None	None	Good

Nonirradiated Maize Oil. Administration of nonirradiated maize oil to 5 infants who had previously manifested untoward symptomatology after viosterol was not followed by any disturbances.

Blood and Urine Findings. Because of the limitations placed upon a clinical study of private office patients, we are unable to present any data on the calcium or phosphorus content of the blood or on urinary analysis.

Duration of Idiosyncrasy. As with other idiosyncrasies, that for viosterol is probably not of a permanent nature. This is well illustrated in 1 infant in our series who received the initial dose of 2 drops 3 times a day at the age of 9 weeks and 2 days later reacted by vomiting and diarrhea. From then on (December 14, 1929) until September 3, 1930, the administration of even 1 drop was followed by the evacuation of loose, watery stools. In the latter part of September, 1930, the mother ventured once more to give 1 drop, and not obtaining any subsequent diarrhea, gradually increased the amount to 20 drops at one dose. There was no reaction for the next 2 months, when we saw the child and advised that the amount be diminished to 15 drops.

Comment. The original investigations of Pfannenstiel⁴ and of Kreitmair and Moll⁵ on the production of ill effects by massive amounts of irradiated ergosterol in animals have been confirmed by others.⁶ We now possess a fairly definite syndrome following the administration of 1000 to 40,000 times the prophylactic dose which may be briefly summarized as follows:

Subjective and Objective. Loss of appetite and lowered food intake; stationary or actual loss of weight; cachexia; diarrhea; diminution in heart rate.

Chemical Alterations. Hypercalcemia; hyperphosphatemia; urine saturated with calcium salts; increased acidity of feces; protein concentration of serum decreased with higher albumin-globulin ratio.

Postmortem Findings. Hypercalcification shown by deposition of calcium in kidneys, lungs, heart, colon, liver and bladder; formation of bladder calculi and grit; vascular injuries consisting of calcification of aorta and arterioles of kidney and suprarenal gland; necrosis of arterioles, especially of kidneys; hypermineralization of bones. In addition to these primary changes, there may be noted secondary reduction in size of the spleen and atrophy of thymus and loss of fat in subcutaneous tissue.

Some of the disturbances have been noted in children by several clinicians⁷ after the use of large doses, but which did not approach the massive amounts employed in the laboratory. These also may be considered from the same viewpoints:

Subjective and Objective. Gastrointestinal symptoms such as diarrhea, vomiting, colic and, in a few instances, constipation; loss of appetite; stationary or actual loss of weight; dehydration and picture of intestinal toxicosis; stupor and peculiar mental state;

pallor; skin rashes and pigmentation; fever; renal irritation manifested by urinary changes such as diminished output, albuminuria, casts and cylinders, presence of red and white blood cells.

Chemical Changes. Hypercalcemia, hyperphosphatemia and hypermineralization of bones.

Postmortem Findings. These are similar to those found in experimental animals but are obviously not as severe. Those reported were in infants who were receiving therapeutic or prophylactic treatment and who died from intercurrent infection.

In contradistinction to this, several clinicians feel that the result of animal experimentation cannot be carried over to infants. A. F. Hess⁸ recently stated that there is little danger of inducing acute poisoning from preparations of irradiated ergosterol and that no harmful consequences would follow if an infant received, through an error, several teaspoons of it. Moore, Dennis and Phillips⁹ feel "that the preparation is as free from toxic effects as ordinary salt." J. Hess and collaborators² studied a large group of infants and found that the administration of 21 to 52 times the prophylactic dose in long feeding experiments and 250 times in shorter periods did not produce any of the ill effects mentioned by others with the exception of constipation and colic. On the contrary, they observed an increase in appetite and a gain in weight which was good, but not in proportion to the food intake. While not denying the possibility of toxic effects in large enough dosage, they consider that their results indicate the wide margin of safety in the use of viosterol. Sobel and Claman¹⁰ did not obtain any unfavorable symptoms with large amounts in either short or long feeding periods, one child receiving as much as 12 mg. of vigantol daily for 80 days. Kostyal¹¹ also reports the absence of any disturbances with both moderate and large doses of vigantol.

While the administration of irradiated ergosterol in prophylactic and therapeutic doses is usually not attended by any untoward symptomatology, our results indicate that mild disturbances may occur in a small percentage of cases with even minute amounts. If we adhere to the definition of idiosyncrasy as a susceptibility in an individual to the action of a drug or food in amounts which are tolerated by the average person, then these instances must be considered as examples of idiosyncrasy to irradiated ergosterol.

It is difficult, however, to determine these limitations because of fundamental differences in the process of manufacture of the various products throughout the world with a resultant variation in strength and dosage. In Germany, the amounts are prescribed in so many milligrams ranging from 0.5 to 10 per day, depending upon the opinion of each individual clinician. Gyorgy⁷ thinks that the amounts usually administered are too large and advocates 0.2 to 0.8 mg. as the prophylactic dose and 1 mg. as the therapeutic, with an increase to 2 or 3 mg. in florid rickets and tetany. If we consider

that 0.5 to 1 mg. of irradiated ergosterol is the equivalent of 7 to 14 teaspoonsful of cod-liver oil, and that 5 mg. represent 70 teaspoons of cod-liver oil, then only can we appreciate what these various doses indicate. An expression of dosage in terms of milligrams, according to Hess,¹ is meaningless. To be of any value, the preparation must be of uniform strength and represent definite amounts of an antirachitic agent. Biologic tests for potency on rats have shown that four widely used preparations made in Germany, United States, France and England bear the following ratio to one another: 2500 to 100 to 80 to 14. The product known as Viosterol, 250 D, which is used in this country is biologically standardized according to the Steenbock method,¹² has a potency of 250 times that of a high grade cod-liver oil, contains 75 vitamin D units per drop and is dispensed with a standard medicine dropper. The prophylactic dose is 10 drops per day and the therapeutic, 15, with larger amounts for rickets and tetany.

It is surprising that the literature contains very little information on idiosyncrasy to this drug, it being mentioned by only a few investigators such as Wiskott,¹³ Eory,¹⁴ Ochsenius¹⁵ and A. F. Hess.⁷ The latter was at first inclined to associate the peculiar symptomatology with a hypercalcemia and an intercurrent infection, but considers "that it is also possible that these children were peculiarly sensitive to the action of irradiated ergosterol."⁷ The only reference to the occurrence of an actual idiosyncrasy which we were able to find is that of Ochsenius,¹⁵ who observed 3 instances and describes in detail the condition in his son who was unable to tolerate even 1 drop without vomiting every time it was given. Other possible examples may be found in Radecourt's¹⁶ 5 patients who showed a pigmentation of the skin on receiving 5 drops 2 times a day for periods of 7 to 25 days. The ill effects after the use of 4 to 10 mg. per day reported by Wiener,¹⁷ Eory,¹⁴ Bernheim-Karrer and Zaruski¹⁸ must be considered from the viewpoint of excessive dosage rather than idiosyncrasy if Gyorgy's and Hess' dosage are accepted as adequate. Likewise the calcification noted by Putschar¹⁹ and by Nikolaeff and Zimble²⁰ may probably be placed upon the basis of an increased susceptibility to irradiated ergosterol during the course of an acute infection rather than upon that of a primary idiosyncrasy. A similar increase of susceptibility in tubercular children is claimed by Bamberger and Stranger⁷ and Dekgwitz,²¹ but this is denied by Gyorgy,⁷ Gehrt-Elberfeld²² and others.

That phase of our experiments which consisted of the administration of nonirradiated maize-oil was an attempt to determine, if possible, whether the ill effects were produced by the irradiated ergosterol or by the oil medium. While inconclusive because of the small number, the results tend to indicate that the disturbances were due to the drug itself and not to the oil medium. This is in keeping with the findings of others. Gyorgy⁷ noted unfavorable

symptoms after the use of both dry and oil preparations and Eory¹⁴ observed a rash following the administration of tablets. A discussion of the identity of the underlying causative factors responsible for the so-called toxic effects in general is outside the province of this communication. The consensus of opinion at the present is that irradiated ergosterol probably contains two separate and individual components—one antirachitic and the other toxic. Windaus²³ and Reerink and van Wijk²⁴ have recently reported the separation of these two factors by chemical means.

Summary. Irradiated ergosterol in the form of viosterol (100 D and 250 D) was administered in doses of 1 to 9 drops a day to 200 infants who were observed over a period of 6 months to 1 year. Untoward symptoms were noted in 15 in the following order of frequency: diarrhea, vomiting, loss of appetite, colic and stationary or loss of weight. No case is included in this group unless a definite sequence was obtained, consisting of administration of the drug, appearance of ill effects, subsidence of the latter on suspension of the drug and finally reappearance on the resumption of viosterol. We feel that the chronological sequence of these events show a definite idiosyncrasy to the drug. One infant lost the intolerance in 1 year.

Conclusions. A definite pharmacologic idiosyncrasy to minute amounts of irradiated ergosterol (viosterol 250 D) exists in some infants. According to the incidence found in our series this is of more frequent occurrence than the literature indicates. The drug should be suspended upon the appearance of any ill effects and permanently discontinued in the event of reappearance of symptoms upon its resumption. The idiosyncrasy to viosterol may not be permanent. We wish to emphasize that the possibility of an individual idiosyncrasy should in no way detract from the general use of irradiated ergosterol in either the prophylactic or therapeutic treatment of rickets.

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SERUM TREATMENT OF 19 CASES OF ANTHRAX INCLUDING ONE OF EXTERNAL, INTERNAL AND BACTEREMIC TYPE.

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ANTHRAX, also known as malignant pustule, woolsorter's disease, charbon, milzbrand and splenic fever, is of extreme interest to physicians and employers in certain industries. It may be said that no industrial disease can have such an insidious onset and produce such devastating results as anthrax. Indeed, it may be so rapid in onset that a person leaving home in the morning in good health to pursue his or her usual occupation may be in a hospital by the afternoon and in the grim clutches of death by the next morning.

It is quite common among the workers of the great leather and wool industries. Philadelphia, and for that matter the entire State of Pennsylvania, is widely known for its tanneries, probably the largest in this country. Persons falling victims to this disease are, as soon as diagnosed or even suspected, sent to the Philadelphia Hospital for Contagious Diseases for treatment and final diagnosis. When it is remembered that the mortality rate is quoted as 10 per cent in external anthrax, 90 per cent in the internal type, and 100 per cent in cases which show a blood stream infection, the importance of early diagnosis and treatment cannot be made too emphatic. In Pennsylvania, out of 123 cases, which occurred in a period of 12 years, 20 per cent died.¹ In our series of 19 cases admitted to this hospital from November, 1928, when I assumed charge of their management, to the present date, we have had the good fortune not to have suffered any deaths.

A total of 25 cases was admitted to this hospital with the provisional diagnosis of anthrax, but only 19 cases were bacteriologically positive. Three might have been called anthrax clinically but were not verified by the bacteriologic reports. Two cases were very definite cases of furunculosis.

Anthrax may be defined as an acute infectious disease prevalent

among animals, especially sheep, cattle, etc., and contracted by man through the handling of infected materials, either directly or indirectly.

Historically it has been traced back to the time when Moses threatened Pharaoh with an epidemic. It is mentioned by such literati as Homer, Virgil, Hippocrates, Galen and Pliny. It took the lives of many animals as well as men. In 1613, 60,000 persons died from this disease in southern Europe. By the end of the sixteenth century it was suspected that this disease was transmitted to man. However, not until 1769 was it first described in literature by Fournier of France.

The causative organism, the *Bacillus anthracis*, was discovered by Koch in 1876, and the vaccine for its treatment in animals was made in 1880 by Pasteur. It is the largest of the pathogenic bacteria, measuring 5 to 10 microns in length and 1 to 1.25 microns thick. It is a spore-forming organism and is one of the most resistant to disinfectants. Spores have been found to survive by Aiello and Drago² for 17 years, and for 18½ years by Busson. It is the first disease of animals and man which was shown to be caused by a microorganism and likewise the first disease against which a bacterial vaccine was found to be effective.

Geographically it is said to be pandemic in distribution. It is more common among the cattle of Siberia, China and other foreign countries. In Siberia it is also known as "Siberian boil plague," while it was described by the Arabian physicians as "Persian fever." On this continent it exists both in North and South America. In man it is most prevalent in the great industrial states of Pennsylvania, New York and Massachusetts, and is endemic in New Jersey and Delaware. It is of interest to note that the first human case on record in the United States occurred here in Philadelphia in 1834.

It is usually contracted by handling contaminated hides, hairs and wool. Contact with such material may be established by the handling of live cattle during the process of skinning such infected animals, or as is most common, in the leather and wool industries. Domestic hides play a negligible part in the spread of this disease. Most infections can be traced to foreign hides.

Many cases of infection through the use of shaving brushes³ have been reported both here and abroad. Cases of soil infection through foot wounds have been reported in Kansas. Infection from person to person is very rare. Dr. S. S. Woody, who has probably seen more cases of anthrax than any single individual in the United States, has never seen a case among the doctors, nurses or attendants in this hospital in a wide experience of 23 years. He has, however, seen a case in a housewife, whose husband was a leather worker, but who had not contracted the disease. Hodgson,⁴ of England, reports a case in a baby, aged 15 months, who contracted the disease from the father, who likewise was suffering from anthrax. McKet-

terick and Pearson⁵ in this country report a case in a child, aged $2\frac{1}{2}$ years, but there is no mention as to the possible source of infection. In view of these facts it seems to me that anthrax is not a highly infectious disease. It surely is not as infectious as epidemic meningitis or infantile paralysis, which diseases are handled in general hospitals. It should be possible, therefore, to treat cases of anthrax in any general hospital, thereby bringing about a more equal distribution of hospital expenditure.

AGE INCIDENCE IN OUR SERIES.

Average age	45.1 years
Youngest age	21 years
Oldest age	68 years

As to the prevalence among the leather and wool industry, our cases showed about an equal distribution.

OCCUPATION.

Leather industry	6
Wool industry	8
Hair and brush	1
Miscellaneous:	
Longshoreman	1
Painter in tannery	1
Carpet weaver	1
Auto-driver, handled rawhides	1
Total	19

Types of Anthrax. The types of anthrax are given as the external and the internal (lungs or intestines). The pulmonary form is brought about by the inhalation of dust impregnated with anthrax bacilli, and is usually seen among the woolsorters, hence the term "woolsorter's disease." The intestinal form is produced by the ingestion, usually, of the spores, which are greatly resistant. It is reasonable to assume that the bacteria make their entrance by the contaminated hands to the mouth. The external type, fortunately, is the most common. This is also divided into the solitary lesion spoken of as the "malignant pustule" and the more diffuse or "malignant edema form." The latter form is usually an indication of poor resistance.

In our series of cases all were of the external type. One case, in addition to the malignant edema form, also had the pulmonary type with bacteremia. The most common sites for the malignant pustule is on the exposed parts of the body. They are, in order of frequency, face, neck, forearm, arm.

LOCATION OF LESION.

Face	7
Neck	5
Forearms	4
Wrist	1
Arms	2
Total	19

A. Battista reports a case in which the lesion was on the penis.

SYMPTOMATOLOGY. The symptoms, of course, depend on the type present. The incubation period is given as 1 to 3 days. This may be much shorter in the internal type or much longer in the external. The first sign of the malignant pustule is a small papule, resembling a mosquito bite. It is accompanied by itching and burning. In 24 hours a small flat vesicle develops with some redness and swelling around it. The vesicle then ruptures exuding a thin, yellowish serum. By the fourth day, a black scab or eschar occupies the place of the vesicle; the edema is more marked and present for a considerable area around the lesion. The eschar is very thick and firmly adherent to the lesion: surrounding this may be seen minute vesicles. If the scab be raised some pus may be seen. Most of our cases were seen in this stage. Only 2 cases were admitted in the early stage, on the second day of the disease, 3 on the third day, 7 on the fourth, 3 on the fifth, 3 on the sixth, and 1 on the tenth day. This gives an average of 4.4 days on admission, and corresponds to the usual anthrax lesion as is commonly seen on admission to this hospital. The lesion varies in size from a 10-cent to a 25-cent piece and is usually solitary. However, cases have been reported where more than one lesion existed in the same patient. As a rule it is free from pain, and in this way may be of help in differentiating it from furuncle and carbuncle. The scab remains for about 15 days. In our series the average number of hospital days was 17.7, the shortest being 12 days and the longest 42 days.

HOSPITAL DAYS.

Average day of disease on admission	4.4 days
Average hospital days	17.7 days
Shortest number of days	12 days
Longest number of days	42 days

The malignant edema form is usually seen on the neck and chest, and the mucosa of the mouth, tongue and eyelid. There is a considerable amount of infiltration and edema of the skin. It is very red and at times definitely purple in color. Scattered over this extensive purplish induration may be found vesicles which vary in size from a pea to a walnut.

The symptoms of the internal type are referable to the pulmonary and intestinal tracts. In the pulmonary form there is pain in the chest, cough, expectoration of bloody sputum and cyanosis. In the intestinal form there is abdominal pain, nausea, vomiting and diarrhea. The constitutional symptoms are more severe in the internal types, and in cases with a positive blood stream infection. In the external type without blood stream infection the temperature seldom reaches 103° F. Only 3 of our cases had a temperature of 103° F. on admission, 1 of which also had a positive blood stream infection. Seven of our cases had a normal temperature, the others ranged between 99.2° and 102.4° F.

TREATMENT. The treatment of anthrax has had many variations since its inception. Originally the attention of physicians was attracted by the local lesion and therefore all treatment instituted tended to destroy the lesion. Fortunately, anthrax remains a local disease for a long time after its onset, thereby offering good possibilities under proper treatment. Every known corrosive and antiseptic of strength has been applied in order that the lesion might be destroyed; this not proving satisfactory, removal of the lesion by the aid of the knife or cautery was practised. In most cases more harm was done by this method, since Nature's barrier of protection was destroyed, and the infection was disseminated into the surrounding tissues.

With the introduction of the antianthrax serum by Marchoux in France in 1895, and Sclavo in Italy in 1903, a new field of treatment was opened. Sclavo himself reported the reduction of the mortality from 24 per cent to 6 per cent in his country. This serum was later modified by Sobernheim, Detre, Ascoli,⁷ and in this country was perfected by Eichhorn. All of our cases were treated with the antianthrax serum. In 1 case in which excision was done and serum given, the results were so discouraging that it has not been attempted since. The patient, a white male, aged 44 years, a fine specimen of manhood, had an anthrax lesion on the neck. In 24 hours after the excision the edema was greater, in 48 hours it descended to the clavicles and spread to the opposite side of the neck, and for a time we feared that respirations might be embarrassed. As a result much larger doses of serum were necessary and much worry was experienced by the staff. However, the patient got well. Seven of our cases, in addition to the serum, were given intramuscular injections of mercury succinimide, beginning with $1\frac{1}{2}$ grains and decreasing the dose every other day, alternating with the serum. However, this was discontinued, for we did not feel that a great deal of benefit was derived from this adjunct. We, therefore, used the serum solely, as best fulfilling the ideals set forth by Dr. Regan:⁸ (1) Treatment must be applicable to the various forms and locations of the disease; (2) have the lowest mortality rate; (3) be specific as possible; (4) possess no danger of generalizing the local infection; (5) offer the least amount of scarring and deformity; (6) cause a minimum of pain; (7) entail the shortest absence from employment.

Our dosage has been larger than is recommended in most textbooks. We have practised the giving of one large dose repeated in 24 hours if necessary, rather than the giving of smaller 8-hour doses. The giving of one dose every 24 hours is more satisfactory for all concerned. It will lessen the painful procedure of venous puncture to the patient, give less risk of accidents, and save time for the medical and nursing staffs. The routine procedure is as follows: After a thorough physical examination the lesion is cleansed with

normal saline and a culture and smear are made from it. It is necessary in cases where the scab is very adherent to elevate it to take material for examinations. A small vesicle may be ruptured and its secretion used for study. The flexor surface of the elbow is then cleansed and properly prepared for the taking of a blood culture. It is better to use the opposite arm when the lesion is on the arm or forearm. The Wassermann needle is inserted and blood removed. The needle is left *in situ* and the warm antianthrax serum is allowed to run in slowly. The dose given is usually 150 cc. intravenously. In no case have we given less than 100 cc. nor more than 250 cc. as the initial dose. Serum is then injected locally. This depends on the location of the lesion. It would be impossible to inject serum locally where the lesion is on the eyelid or lip; but if on the neck, arm or forearm it can be given easily. The amount of serum locally injected in our cases ranged from 30 to 50 cc. Four points are selected in the different quadrants of a circle, making sure that the injection is fairly wide of the lesion, so that no infection is pushed into the surrounding tissue. For the next 24 hours there will be noticed an increase of the edema surrounding the lesion; but in 48 hours this will begin to decrease, so that by the end of 7 days the edema and blisters will have cleared up and the black eschar only remains.

AMOUNT OF SERUM GIVEN.

Average amount	498.4 cc.
Smallest amount	200 cc.
Largest amount	1050 cc.
Average number of injections	3
Smallest number of injections	1
Largest number of injections	6

The question of serum disease is practically negligible. Only 1 of our patients developed a serum rash; and 4 patients developed chills immediately after or from 1 to 2 hours following the intravenous use of the serum. These were easily handled by the giving of warm drinks, hot-water bags to the body, and adrenalin hypodermically.

May I now give more in detail the report of 1 case presenting this extraordinary combination: external and internal (pulmonary) anthrax with bacteremia and recovery?

Case Report. CASE 1.—S. R., aged 63 years, male, white, a woolworker, was admitted to our Hospital December 7, 1929, extremely ill in the fourth day of his disease. His temperature was 103.8° F., pulse 110, respirations 32. He first noticed the appearance of a small pimple on the right wrist 3 days previous to admission. The lesion became larger and he noticed a beginning discoloration. He was treated in the dispensary of a general hospital. The lesion extended up the arm, a black scab formed. He had a slight fever for 2 to 3 days.

His family history was negative. He had had tetanus in 1923.

Physical Examination. A well developed but poorly nourished white adult, gray hair and beard. His face had an anxious and dusky appearance. His cheek bones were prominent and the temporal regions quite hollow. The temporal vessels were very tortuous.

Head and Neck. Scalp negative, ears negative, nose negative, tonsils small but diseased. Eyes, moderate arcus senilis. Teeth, poor condition, many missing. Neck, negative.

His chest gave the signs of a moderate emphysema with some impairment to percussion at the bases and a few moist râles at both bases. He expectorated a grayish-white sputum but not blood-tinged. The right axillary nodes were enlarged.

Heart. No visible cardiac impulse. The apex beat could be heard in the fifth interspace in the mid-clavicular line. There was no apparent enlargement, heart sounds of poor quality, rhythm irregular, at times suggestive of fibrillation, a pulse deficit was present.

Abdomen. Negative.

Extremities. Right upper extremity presented on the anterior surface of the wrist a lesion about the size of a 25-cent piece surrounded by an area of redness 3 inches in diameter, upon which could be seen many vesicles about the size of a pea, filled with a clear yellow sanguinous liquid. On top of the lesion, centrally located, could be seen a hard, adherent, thick, black scab or eschar. Leading toward the elbow could be seen a brawny edema extending upward one-half distance of elbow to the shoulder. The color at places was almost purple. The radial artery was very much sclerosed. The pulse irregular, poor volume and feeble. The lower extremities presented marked varicosities.

Procedure. The patient was put to bed, culture and smear of lesion and blood culture were taken. One hundred and fifty cubic centimeters of serum were given intravenously and 50 cc. around the lesion. Shortly after the giving of serum the patient had a mild reaction: chill, temperature 105.2° F. He was given 10 min. of adrenalin, hot-water bags to body, morphin sulphate, $\frac{1}{4}$ gr. Patient was relieved. The following morning, December 8, 1929, he was very much improved. The temperature was 100° F.; pulse, 70; and respiration, 32.

One hundred and fifty cubic centimeters of serum were given intravenously. To offset the possibility of an immediate serum reaction this was preceded by whisky, 1 ounce, and adrenalin 10 min. Patient had no reaction. On account of the irregularity of the heart, digitalin, 15 min. every 4 hours for 2 days was given. It must be remembered that although the pulse rate was 70 per minute, the heart rate was 110 per minute, the temperature was 103° F. On the morning of December 9, 1929, 130 cc. of serum were given intravenously and again preceded by whisky and adrenalin. One hundred and fifty cubic centimeters were to have been given but 20 cc. were lost during the operation. The temperature showed a very definite decline so that by the morning of December 10, 1929, it was 99.6° F. The patient felt better. Edema of the arm remained the same. At 9 P.M. he complained of pain in the right hand and discomfort in the chest. He expectorated a mucopurulent sputum which was blood-tinged. The temperature remained the same. The sputum was found positive for anthrax bacillus. The next morning the temperature was 103° F., pulse 50 per minute. He complained of pain in the chest. A pleural friction rib was found at the level of the sixth rib in the right posterior axillary line, many crepitant râles could be heard throughout the right base. His color was cyanotic and we were much alarmed. One hundred and fifty cubic centimeters of serum were given intravenously preceded by whisky and adrenalin. Tincture of digitalis, 20 min. t. i. d.; quinin sulphate, 5 gr. daily; morphin sulphate, $\frac{1}{4}$ gr. to control pain and as a sedative. The next morning the temperature was 99° F. The patient was given 150 cc. more of serum. Edema of the hand was very definitely less and lesion was drying. The serum was then discontinued. The patient was much improved, more comfortable, his chest condition clearer, and had a normal temperature until December 15, 1929, when he again had a rise of temperature (99° F.) and a blood-tinged sputum. One hundred and fifty cubic centimeters of

serum were again given. From this day on the patient made a rapid recovery. The temperature was normal and the pulse ranged between 70 and 80 per minute. On December 23, 1929, digitalis was discontinued. He was allowed up in a chair and the lesion was rapidly disappearing. He was discharged January 18, 1930.

Laboratory Studies. Urine showed a faint cloud of albumin and occasional white blood cells. Culture of lesion, culture of blood and smear from the lesion were positive for anthrax. The sputum was positive from December 11 to December 15, 1929. Blood culture and smear from lesion were negative on December 11, 1929.

The total amount of antianthrax serum given this case was 930 cc.

The treatment of anthrax would not be complete without a word as to the other remedies which are now in vogue. Krouse,⁹ of Argentina, reports the treatment of 200 cases in which the mortality was 0.5 per cent. His treatment consisted in the use of normal beef serum. The bacteriophage of D'Herelle has been used with good results by Villega Ruiz.¹⁰ Adrianus Pijper¹¹ reports the use of neoarsphenamin in 40 cases without a single death. He states that the anthrax patient can stand large doses of arsenic. His initial dose is 0.9 gm. and repeated the next day. Usually three doses only are required.

Conclusion. 1. In our experience large 24-hour doses of anti-anthrax serum given early, and as often as is necessary, will cure most cases.

2. The lesion itself should not be molested; but the local injection of serum is to be practised when possible.

3. Our experience with other forms of treatment is very scanty, but neoarsphenamin has apparently given good results.

4. In 19 cases, including 1 with pulmonary infection and bacteremia, this has been uniformly successful.

5. We prefer to give a large intravenous dose (100 to 250 cc.), repeating in 24 hours as necessary, followed by local injections of 30 to 50 cc. Our cases received an average of 500 cc. (extremes, 200 to 1050 cc.) in from one to six injections.

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PREGNANCY AND DIABETES, WITH A REPORT OF 5 CASES AND A REVIEW OF THE LITERATURE.

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IN presenting additional case reports of patients with pregnancy and diabetes, it seems useful to include with them a review of the literature since insulin has come into common use. Since the question of the effect of pregnancy upon diabetes is still controversial, we were particularly interested in analyzing case histories from that standpoint. In the selection of this material from the literature we have chosen only such data that seemed adequate for this type of study.

The position of the physician relative to pregnancy in the diabetic patient, either when present or premeditated, is a difficult one. Diabetes may endanger both the life of the mother and the child, even in spite of careful medical management. The diet, insulin dosage, body weight of the mother and the presence of hyperglycemia or hypoglycemia during pregnancy demands especial attention and constant watching. The woman often asks, "Will my child be a diabetic or will it be liable to develop diabetes?" There seems to be no evidence as yet that the children of diabetic mothers are more liable to diabetes, although a few isolated instances have appeared in the literature.

Case Reports. CASE 1.—Mrs. E. H., a multipara, aged 39 years, was admitted to the hospital on November 25, 1929, because of pregnancy (3 months) and sugar in the urine which had been discovered during a pregnancy which had occurred in 1928. Diabetes mellitus had been considered to be the cause of the glycosuria and was readily controlled by dietary restriction. She passed through a normal pregnancy and puerperium. She remained on a "somewhat restricted diet" and was in good health until April, 1929, when she noticed fatigue and loss of weight. Her last menstrual period was in August, 1929. Upon admission she stated that her diet had been rather low over a period of months, her urine was free of sugar and a fasting blood sugar was 125 mg. On the first day in the hospital she was given a diet of 120 gm. carbohydrate, 60 gm. protein and 130 gm. fat, which promptly brought on glycosuria—40 gm. in the first 24 hours. The diet was then reduced to 100 gm. carbohydrate and 18 units of insulin were given daily. She was discharged from the hospital with a diet of 120 gm. carbohydrate,

75 gm. protein and 135 gm. fat with 26 units of insulin daily. Her urine was sugar free, except for an occasional trace, and her blood sugar during digestion was 179 mg. Two weeks after discharge to the care of her home physician the pregnancy was terminated. Soon after this mild insulin reactions occurred and the insulin dosage was gradually reduced to 8 or 10 units daily. She had remained well and the diabetes has been kept in control since.

Comment. One cannot be certain about the effect of pregnancy on tolerance, but there does appear to be a lessened insulin requirement after the termination of pregnancy.

CASE 2.—Mrs. D. B., aged 21 years, was admitted to the hospital, February 9, 1927, because of thirst, craving appetite and loss of weight, which had been present only a month. Her blood sugar was 620 mg. per 100 cc. and the urine showed moderated ketosis. She remained under hospital supervision for 10 days. The glycosuria and hyperglycemia responded rapidly to treatment with a diet of 50 gm. carbohydrate, 60 gm. protein and 130 gm. fat with 20 units of insulin daily. She was discharged with a diet of 75 gm. carbohydrate, 60 gm. protein and 150 gm. fat and 20 units of insulin daily. During the next six months she was seen several times; her diet was gradually increased to 105 gm. carbohydrate and the insulin was reduced to 16 units. By July her weight had increased from 100 to 111 pounds. She was not seen again until March, 1930, when she announced that she was 3 months pregnant and that in order to keep her urine sugar free, since the inception of pregnancy, it had been necessary to increase the insulin 27 units daily. Her fasting blood sugar was 98 mg. and the urine gave a negative Benedict test. She has not been seen by us since that time. In November, 1930, she wrote the following letter: "My baby was born September 6. It weighed 8 pounds and 3 ounces. I came through my pregnancy in fine shape, but had to double my insulin to keep my urine sugar free. After the baby's birth I decreased my insulin to 20 units daily and was able to eat more on that amount of insulin than previously. However, since I have stopped nursing the baby I find that I cannot take as much food without having sugar in the urine. I weigh the same as I did before pregnancy. I am watching the urine very closely."

Comment. Although this patient was not under hospital supervision during the pregnancy and puerperium, it would seem that her observations were fairly accurate and the happy outcome indicates that she watched her own management very strictly. Pregnancy in this case probably reduced the patient's tolerance while the lactating period increased it.

CASE 3.—Mrs. B. F., aged 23 years, was admitted to the hospital, April 30, 1928. She stated that she had no complaint at this time, but that on February 20, 1928, she had given birth to a full-term, dead baby; that when she was 6 to 7 months pregnant she developed extreme thirst, passed a great deal of urine and had to get up frequently at night to void. Her physician had said that her blood sugar was high and that her diabetes should be studied in the hospital. Upon admission sugar was found in the urine and the fasting blood sugar was 225 mg. On a test diet of 1700 calories she excreted about 30 gm. glucose. She remained under observation for 8 days, when she was discharged with a diet of 80 gm. carbohydrate, 60 gm. protein and 130 gm. fat and 23 units of insulin daily. Her diabetes was well controlled. She then visited the outpatient department frequently and proved to be very coöperative. Her diet was increased to 95 gm.

carbohydrate and the insulin reduced to 16 units. During 1928 she had amenorrhea from June to November without evidence of pregnancy. In April, 1929, her menstruation again ceased, and two months later pregnancy was diagnosed. She visited the outpatient department regularly, and remained in excellent condition. Her urine was always free of sugar, and the digestive blood sugar was usually under 150 mg. The diet and insulin dosage remained constant, and it was not until the sixth month that she began to gain weight—105 to 116 pounds at full term. She was delivered at home by her family physician, February 7. Her baby weighed $5\frac{1}{4}$ pounds and thrived. She visited us in March, when we found her urine to be free of sugar, blood sugar 163 mg. during digestion and weight 103 pounds. She then stated that it had been necessary to reduce the insulin from 16 to 10 units daily since delivery because of mild reactions. Her program has not been changed for a year and she has remained well.

Comment. In this case pregnancy did not exert any striking change in the insulin requirement; however, since delivery she is able to get along with 6 units of insulin less. It is to be noted that there was very little change in her body weight and that her baby was small.

CASE 4.—Mrs. M. B., aged 25 years, was first seen in January, 1927, because of thirst and loss of weight, which had been present 1 month. Diabetes mellitus was diagnosed because of fasting hyperglycemia and glycosuria. She was started with a low diet—50 gm. carbohydrate, 60 gm. protein and 130 gm. fat—and because sugar was excreted in significant traces, it was increased very gradually in spite of the normal fasting blood sugar. By April she was taking 90 gm. of carbohydrate and 170 gm. of fat. Her fasting blood sugar remained normal but slight glycosuria persisted. Her weight, which had been 137 pounds, dropped to 127 pounds in the course of 4 months' treatment. In June, because of hyperglycemia, glycosuria and further loss of weight and strength, insulin was started—5 units before breakfast. During the next year the insulin dosage was gradually increased until she was taking 60 units daily in order to control glycosuria. During this period she regained her weight, whereupon the diet was reduced to 130 gm. fat and the insulin dosage gradually lessened to 36 to 40 units daily, which seemed to be minimum amount which would keep her urine sugar free. Her blood sugar taken at about 11 A.M. was usually about 100 mg., and she at times experienced mild insulin reactions. In April, 1929, her menstruation ceased, and morning sickness appeared in May. Beginning with the fifth month of pregnancy, it became necessary to increase the insulin because of heavy, persistent glycosuria, and by October she was taking 122 units daily. In December, just before delivery, 138 units were being taken. She remained in excellent clinical condition; her weight increased from 140 to 163 pounds during the pregnancy. She was delivered without difficulty at 4 A.M. on December 22, with chloroform anesthesia; at 6 A.M. she complained of being very hungry and was given 100 cc. of orange juice. Two hours later her blood sugar was 87 mg. The diet remained the same, but the insulin dosage was sharply reduced from 138 to 84 units daily. In spite of this she had very severe insulin reactions during the next three days, even though the insulin had been further reduced to 60 units. The diet was then increased to 110 gm. carbohydrate and the insulin reduced to 50 units daily. After her return home she found it necessary to further reduce the dose to 38 units daily in order to eliminate reactions. In March, 1931, her fasting blood sugar was 134 mg.; during digestion, 161 mg.; weight, 144 pounds. Her present diet is 110 gm. carbohydrate, 60 gm. protein and 90 gm. fat. Insulin dosage, 38 units daily.

Comment. This patient has true diabetes mellitus, apparently with a lower renal threshold than is usually seen. She exhibited a remarkable tolerance for insulin during pregnancy; possibly she would have done just as well if mild, persistent glycosuria had been permitted. Immediately after delivery her insulin requirement dropped at least 60 per cent and she had severe insulin reactions which she had not experienced during pregnancy.

CASE 5.—Mrs. E. F., aged 26 years, was first admitted in November, 1927. She had had symptoms referable to diabetes for about a year and had lost 75 pounds in weight. She was in diabetic coma, but responded very rapidly to treatment. She stated that she had menstruated but twice in her life—a little more than a year ago—and that these periods were very scant. She presented a rather extreme degree of male hair distribution and had an extensive furuncular infection in the anogenital region. Her weight was 163 pounds. Upon discharge, two weeks later, her urine was sugar free, blood sugar during digestion 146 mg. and she was instructed to take 50 units of insulin daily. She was not seen again until February, 1929, when she was readmitted in a state of impending coma, with infection of the skin in the anogenital region. Insulin had been taken rather irregularly since discharge a year ago and none had been taken during the past month. She was discharged in good condition 2 weeks later with about the same insulin-diet program as previously. Nothing was heard from her until October 2, 1929, when she was admitted on the obstetrical service, 5 months pregnant. The management of her diabetes had been irregular, but the insulin in varying dosages had been continued and she apparently had been having severe reactions, which she had never had before. The diet, 100 gm. carbohydrate with 1700 calories, was continued, and she was discharged 4 days later, taking 40 units of insulin daily. Three days later she was again admitted, unconscious. The diagnosis seemed uncertain, but as she regained consciousness after the use of glucose proctoclysis, it may reasonably be assumed that she was in a state of insulin coma. The dosage was then reduced to 25 units. This patient was not seen again until January 28, 1930, when she entered the hospital in impending coma. We afterward learned that food and insulin had been stopped 2 days prior to admission because several teeth had been removed. Prior to this she had continued to have insulin reactions and was often unconscious. She had been vomiting and had had epigastric pain for 24 hours. The first examination showed moderate hyperpnea, evidences of dehydration and a subconscious state. Her blood sugar was 358 mg. and the CO_2 capacity of the plasma was 11 vol. per cent. The leukocytes were 26,000, with 89 per cent polymorphonuclears. Her pregnancy was at full term or nearly so. The fetal heart sounds were faintly audible. Immediately upon admission she received 30 units of insulin and 500 cc. of 5 per cent glucose subcutaneously. After this a Cesarean section was done under light ether anesthesia in an attempt to save the child. There was considerable anesthetic fluid. The baby was cyanotic and was resuscitated with difficulty, and lived only a few hours. The mother was treated as a case of diabetic coma and had a rather stormy period of several days. On the sixth day she was able to take a regular diabetic diet of 90 gm. carbohydrate, 70 gm. protein and 100 gm. fat, but it required 70 units of insulin daily to keep the urine in most of the specimens free of sugar. She was in good condition 2 weeks after admission, taking 60 units of insulin daily. That we would not see the patient again until she encountered further difficulties, we advised her to reduce gradually the insulin dosage as long as her urine remained fairly free of sugar. We have not heard from the patient since.

Comment. We had opportunity to observe this patient before, during and for a short time after pregnancy. It would appear that her insulin requirement was considerably less during the later months of pregnancy, and even though the insulin dose was sharply reduced she continued to manifest sensitivity to it. The complete withdrawal of insulin at the eighth month for 2 days caused diabetic coma.

The data obtained from the literature review were so voluminous that it seemed practical to present here only a condensed form. The following data include our own cases:

TABLE 1.—DATA ON DIABETES AND PREGNANCY.

Total number of pregnancies	73
Total number of patients	66
Patients requiring insulin continuously	49
Maternal mortality	6 (9%)
Causes of maternal death, each 1 case: diabetic coma at term; diabetic coma with toxemia of pregnancy; death occurred suddenly 4 days postpartum, unexplained; insulin shock, 5 days postpartum; eclampsia; sepsis following gangrene of the arm.	
Total number of living children	46 (63%)
Total number of fetal deaths	27
Stillbirths, at term	13 (50%)
Spontaneous abortions and premature births	10 (35%)
Therapeutic abortions	4 (15%)
Diabetes developing or discovered during pregnancy	18
Instances of diabetic coma developing during pregnancy	13*
Instances of acidosis or coma associated with fetal death	13*
Case reports which could be analyzed with regard to the following data	43
Patients who required more insulin during pregnancy	28
Patients who required more strict diets during pregnancy	2
Patients requiring more insulin during pregnancy and less during the puerperium	20
Patients requiring the same amount of insulin during the pregnancy but less in the puerperium	1
Patients requiring more insulin during both pregnancy and puerperium	5
Patients requiring less insulin during pregnancy	10
Patients, not insulin treated, but showing a higher tolerance late in pregnancy	3
Patients requiring less insulin during the pregnancy but more during the puerperium	6
Patients requiring less insulin both during the pregnancy and puerperium	1
Weight of babies at full term (in many case reports this is not given):	
Below 7 pounds	14
Between 7 and 10 pounds	19
Over 10 pounds (2 were 13 pounds)	3

* Only 1 case was found in which the mother had extreme acidosis and the child lived. The disparity between the 2 figures is because 1 case reported only as "acidosis" is not included as a coma case; the child was lost in that instance.

Discussion. In making this statistical study of the available literature we have selected only those reports which included fairly complete data. In the majority of instances the publications have been made by physicians whose interest was in internal medicine and not in obstetrics. Therefore, we may reasonably assume that patients in this series have, for the most part, had the benefit of

experienced management and represent a cross section of patients with pregnancy and diabetes as they occur in our well-equipped hospitals and clinics.

Maternal Mortality. Unfortunately we have not found any large series of case reports concerning the maternal mortality before the insulin period. Hirschfeld,¹ however, estimated this at 50 per cent, and Williams² in his 66 patients reported that 27 per cent died during delivery or soon after. Also, diabetic patients frequently became sterile, so the relative incidence of pregnancy in diabetics was then not as great. The mortality of the mothers in this collection of cases during the insulin era is 9 per cent, which from the standpoint of the obstetrician is still high. However, as one scans the causes of death it will be seen that a number of them were accidents and could probably have been prevented if the proper relationship between the patient and her physicians had existed.

Infant Mortality. We were also not able to find any extensive statistics of the effect of diabetes on the fetus. Joslin's³ series contains 89 cases from 1898 to 1928. We assume that the majority of these occurred before insulin was used. Of these there were 42 living children, 14 stillbirths, 13 miscarriages and 6 therapeutic abortions. Both Williams and DeLee,⁴ in the older editions of their books, state that the fetal mortality was about 66 per cent. In the present insulin group the fetus had a better chance for survival, as 63 per cent of the pregnancies resulted in living children. This, however, from the viewpoint of the obstetrician is high. The stillbirths at term are responsible for 50 per cent of fetal deaths. It seems very probable to us that acidosis is in a large measure responsible for fetal deaths, as but 1 patient in the entire group who had coma gave birth to a living child and she was delivered rather promptly after admission by Cesarean section. Mild acidosis may be sufficient to kill the fetus when coma is not produced in the mother. One of our patients had 2 miscarriages several days after attacks of pre-coma.

Weight of the Fetus. The average weight of 37 full-term fetuses, those whose weights were obtainable, was 7.93 pounds, whereas the average weight of the normal baby at birth is 7.25 pounds. This is in accord with previous statements, that the weight of babies of diabetic mothers had a tendency to be greater than the average normal.

The Effect of Pregnancy on Diabetes. The average diabetic woman during pregnancy is probably under closer supervision by her physicians and by herself than she is at other times, and possibly under such circumstances it might be expected that her diabetes would show improvement. However, it has been our experience that there usually is a decreased tolerance during that period; others have felt that tolerance is considerably improved. One of our patients (Case 5) did show quite striking sensitivity to insulin

in the latter part of pregnancy. From the literature we were able to select 43 case reports which could be analyzed with regard to the effect of the pregnancy on diabetes. Of these 70 per cent seemed to show the equivalent of a reduction of tolerance, *i. e.*, the insulin had to be increased or the diet had to be reduced. In the majority of these the insulin had to be reduced or the diet increased during the puerperium. This change of insulin requirement is most strikingly demonstrated in Case 4 of this series where the insulin dosage was increased from 40 to 138 units daily during pregnancy without the occurrence of reactions, then reduced after delivery to 84 units and finally back to the original 40 units daily before insulin reactions ceased. We have attempted to correlate increased insulin requirement with increased weight of both the mother and the baby, but could find no satisfactory relationship. It then appears to us that clinical observation supports the view that there is an increased insulin demand during pregnancy for which there is no adequate explanation. Possibly pregnancy produces a metabolic or hormonal anti-insulin substance. This view receives further substantiation in the following observations:

1. Before insulin pregnancy carried with it a very high mortality rate in the diabetic.

2. Joslin and White report that 33 of their 89 pregnancy diabetic patients developed diabetes during pregnancy. In this series diabetes was discovered or developed in but 18 of the 66 patients during pregnancy.

3. Coma, which is usually the result of temporary diminution of tolerance, developed in 18 per cent of the patients in this series, usually near the end of pregnancy.

It has been difficult to reconcile these clinical observations with the experiments of Carlson⁵ and his coworkers whose work has been so generally referred to. In 1923 Simon, Stulz and Aron⁶ repeated these experiments and also concluded that the placenta was probably permeable to insulin and that the insulin from the fetuses protected the mother. Aron⁷ later on, however, by the use of insulin injections reached the opinion that insulin was not passed through the placenta. The experiment of Macleod⁸ is of great interest in that it conforms to some clinical observations. He allowed a depancreatized bitch that was on a standardized insulin-diet program to become pregnant. Hyperglycemia and glycosuria continued throughout gestation, but there was no remarkable increase of glucose excretion. Unfortunately, he does not state the sugar excretion for but a few days before impregnation. The day following the birth of the pups the mother had an insulin reaction and her blood sugar was found to be 67 mg. Her glucose excretion dropped from between 30 and 50 gm. daily to less than 5 gm. during the time she was suckling her young. The experimental observations of Britton⁹ on the maternal and fetal blood

sugar changes are also in keeping with our clinical observations. In one case a cat gave birth to four kittens during severe hypoglycemia with no symptoms of a hypoglycemic reaction. The same dosage of insulin produced convulsions a few weeks later. He felt that his study indicated that the blood sugar of the fetus was adjusted to emergency conditions that might be imposed on the mother. Schlossman¹⁰ has recently reported experiments of anesthetized pregnant dogs and cats which were immersed in warm salt solution, the uterus opened and the fetuses delivered into the solution, leaving the placental circulation intact. Some of the fetuses were injected with large amounts of insulin (40 to 80 units) either intraperitoneally or into the umbilical artery. The mother's blood sugar was lowered very slightly as compared with the intravenous injection of one-tenth the amount of insulin that was injected into the fetuses. The maternal blood sugar was found to rise slightly after the death or the detachment of the fetuses. The blood sugar of the fetuses was at a hypoglycemic level at the end of 4 or 6 hours. He concludes that the placenta of the dog and cat are impermeable to insulin and that the slight lowering of the mothers' blood sugar was due to the utilization of the mothers' glucose by the fetuses. Relative to the point of the possible effect of the fetal insulin on the mother's metabolism, or *vice versa*, we have found instances of hypertrophic islands of Langerhans in the fetuses of diabetic women—the case reported by Gray and Feemster,¹¹ in one by Dubreuil and Anderodias,¹³ the one by Wiener¹² and our Case 5. Of these 2 had an improved tolerance during pregnancy, 1 required more insulin and on the other the data were not sufficient.

It would seem then that the whole subject of carbohydrate metabolism during pregnancy is exceedingly complex and that there are no general rules to guide one, except that each patient must be treated individually with the reasonable expectation that her insulin requirement during pregnancy will increase. Also, it seems wise to reduce the insulin during the puerperium, especially if it has been markedly increased during the pregnancy. Lactation, with its diversion of 20 to 30 gm. of glucose daily in the form of lactose, may quite likely contribute to this phenomenon.

Summary. 1. Insulin as it is used today has markedly lowered the mortality rate of the pregnant diabetic woman and considerably enhanced the chances of preserving the life of the baby. Both of these improvements, however, are far from the obstetrical ideal.

2. The greatest danger for both the mother and the child is acidosis and coma.

3. There seems to be a great variability of tolerance and insulin requirement during both the pregnancy and the puerperium. The nature of this is without adequate explanation. The clinical evidence supports the view that pregnancy increases the severity of the diabetes, at least temporarily, in the majority of instances.

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RENAL GLYCOSURIA.

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A RECENT critical analysis of 9000 consecutive cases of glycosuria observed by Dr. Elliott P. Joslin and associates, for the most part over a long term of years, has revealed only 15 cases of "renal glycosuria." This low incidence merits further consideration and explanation as to the diagnostic standards used.

Although more than 35 years ago Klemperer¹ and Lepine² called attention to the occurrence in man of glycosuria without hyperglycemia, there is still disagreement as to the clinical features

essential for the diagnosis of the condition known variously as renal diabetes, orthoglycemic glycosuria and renal glycosuria. In a complete review of the literature Hjärne³ quotes Hatlehol as stating, in 1926, that he had seen "close upon" 100 cases of renal glycosuria. Falta⁴ states that since 1922 he has seen 85 cases of renal diabetes. Salomon,⁵ Maclean⁶ and Hjärne³ do not regard the condition as extremely uncommon. On the other hand, Rabino-witch⁷ and Fitz⁸ believe that it is very rare. The difference in reported experience depends probably to some extent on the personal interest of the individual clinician. Nevertheless, a review of the literature^{4,9,10} shows that the largest part of the difference is undoubtedly due to varying diagnostic standards. Consequently, any discussion of the subject must be prefaced by a statement of criteria which have been used in selecting the cases reported.

In the fourth edition of *The Treatment of Diabetes Mellitus*¹¹ Joslin recorded 47 cases of renal glycosuria in the first 6000 cases of glycosuria. In the next 3000 cases (to March, 1930) 19 more were so classified, making 66 in all. As a result of later observations and the recent study, these 66 cases have been regrouped as follows:

	Cases.
"Typical" renal glycosuria	15
"Atypical" renal glycosuria	7
Chronic ("essential") pentosuria	2
Renal glycosuria of pregnancy	6
"Unclassified glycosuria" in which constant glycosuria has been disproved	19
Miscellaneous group, discarded for the present because of too short period of observation, insufficient data, etc.	17
	<hr/> 66

Groups 1 and 2 are reported in some detail in the present paper. Group 3 is reported in the following article.¹² Groups 4 and 5 are dismissed because glycosuria was not permanent. It is probable that in Group 6, which is for the present discarded, there are certain cases of "typical" renal glycosuria.

The finding of 2 cases of pentosuria illustrates well, as has been emphasized by Jones and Sussman,¹³ the clinical similarity of renal glycosuria and pentosuria. It shows the importance of attempts to identify the type of sugar which is being excreted by patients with supposed renal glycosuria.*

Diagnostic Criteria. The following standards were chosen arbitrarily in the selection of the cases of "typical" renal glycosuria here reported.

1. Glycosuria without hyperglycemia. Sugar should be found in every specimen of urine examined, whether it be voided in the fasting state or after a meal. The amount of sugar excreted per 24 hours is of little importance; it may be large (over 100 gm.) or small (under 10 gm.). No fasting blood sugar value (venous)

* Since this paper was completed an additional case of pentosuria (in a child) has been discovered.

may be 0.12 gm. per 100 cc. or over and no blood sugar value (venous) after a meal may be 0.17 gm. per 100 cc. or over.

2. Glycosuria should be largely independent of diet, but may fluctuate somewhat, depending on the amount of carbohydrate ingested.

3. The level of blood sugar should be influenced only slightly by the ingestion of food. The curve obtained after the giving of 100 gm. of dextrose should be a normal one with no value rising to 0.17 gm. per 100 cc. or over and with a return to the control value within 2 hours. Often the tolerance curve may exhibit even less than a normal rise.

4. The symptomatology characteristic of diabetes mellitus should be absent.

5. The type of sugar found in the urine should be proved to be dextrose and not levulose, pentose or other substances which reduce alkaline copper solutions.

6. No progression toward true diabetes mellitus should be evident during an arbitrarily chosen period of at least 3 years of observation.

7. For complete study it should be shown that the patient is able to store and utilize carbohydrate in a normal fashion as demonstrated by determinations of the respiratory quotient and metabolism before and after a carbohydrate meal. We have not carried out this desirable procedure. As Rabinowitch¹⁴ and Paullin¹⁵ have shown, however, the mild diabetic under certain conditions may show no impairment by such tests, so that the method does not afford an absolutely reliable means of differentiating mild diabetes from nondiabetic glycosuria.

8. A common finding,³ which cannot, however, be regarded as a necessity for diagnosis, is the history of glycosuria occurring in the relatives of the patient.

Methods Used. 1. *Urinary Sugar.* Practically all the qualitative tests were performed by Benedict's method, although in a few of the earlier tests Fehling's and Nylander's reagents were used. The amount of sugar was determined in the earlier tests by the fermentation method, by polariscope and by Benedict's original method. Since 1922 all quantitative determinations have been carried out by Smith's modification¹⁶ of Benedict's method.

2. *Identification of Type of Urinary Sugar.* Seliwanoff's reaction for levulose and Tollen's phloroglucinol test for pentose were used¹⁷ to exclude the presence of these sugars. The fermentation test was applied in the usual manner, using bakers' yeast and incubating in a saccharometer for 12 to 24 hours at 25° to 30° C. In every instance after allowing time for fermentation the Benedict test was repeated to assure the complete disappearance of reducing substances. In a few instances (see Table 1) the phenylhydrazine test¹⁸ was carried out and the osazones so formed identified under the microscope. In a few instances (see Table 1) after recrystallization the melting point of the crystals was determined.

TABLE 1.—CASE SUMMARIES OF 15 CASES OF

Case No.	Sex.	Glycosuria in family.	Age of patient.				Duration of glycosuria to date, years.	Urinary sugar.				Last examination of urine.*					
			Glycosuria first noted.	When first seen.	Age, December, 1930.	Range.				Date, 1930.	Albumin. †	Sediment §	Sugar, per cent.	Pentose.	Levulose.		
						Low, per cent.		High, per cent.	Recorded urine examinations.							Recorded sugar-free examinations.	
a. Patients With																	
2165	M	2 children	10.2	37.9	46.7	36.5	0.9	5.3	44	0	Dec.	VST	Negative	2.0	0	0	
2279	M	Great-grand mother	17.8	17.9	27.3	9.5	0.2	6.4	55	0	Dec.	VST	Negative	4.0	0	0	
2768	F	16.7	26.0	34.4	17.7	Tr.	3.3	19	0	Nov.	VST	Negative	1.2	0	0	
3618	F	Mother; sister	16.3	16.4	23.3	7.0	0.3	0.8	10	0	Dec.	VST	5-15 WBC; p.h.p.f.	0.6	0	0	
4025	M	Brother	41.3	41.4	47.8	6.5	0.3	5.3	20	0	Sept.	SPT	Negative	5.3			
4160	F	Mother; father; 3 pat. uncles	6.2	6.2	12.3	6.1	0.2	5.0	24	0	Dec.	VST	Negative	5.0	0	0	
5745	M	Father; brother	15.5	15.6	19.5	4.0	0.1	1.8	18	0	Dec.	SPT	Negative	0.6	0	0	
6252	F	Mother; brother; sister	25.9	35.7	39.0	13.1	0.4	2.5	10	0	Dec.	VST	Rare RBC; 10-25 WBC; p.h.p.f.	0.4	0	0	
6314	M	Pat. uncle	28.1	28.1	31.3	3.2	0.3	1.4	6	0	Dec.	VST	1-4 WBC; p.h.p.f.	0.4	0	0	
6708	F	Sister	4.8	5.5	8.3	3.5	0.2	3.8	48	0	Dec.	VST	Negative	2.7	0	0	
6709	F	Sister	5.6	6.4	9.3	3.7	0.3	3.4	46	0	Dec.	VST	Negative	3.4	0	0	
8356	M	33.8	43.6	44.8	11.0	Tr.	0.5	6	0	Dec.	VST	Rare WBC; p.h.p.f.	Tr.	0	0	
8357	F	19.2	21.1	22.3	3.1	0.3	3.8	8	0	Dec.	VST	Negative	0.4	0	0	
8834	M	28.7	31.8	32.5	3.8	0.3	2.2	9	0	Dec.	VST	Negative	0.5	0	0	
8885	M	Father	27.7	37.8	38.6	10.9	0.2	2.8	8	0	Dec.	ST	3-5 WBC; p.h.p.f.	0.4	0	0	
Averages and totals 15 cases	M-8 F-7	Hereditary cases—11	19.9	24.8	29.2	9.3	0.3	3.3	22	0	2.2
b. Patients With																	
1266	M	Mother; sister; 1 mat. aunt; 2 pat. great-aunts	5.4	6.9	11.9	6.5	0.0	1.7	160	6	Sept. 1919	0	Negative	0.3			
1612	F	Sister of No. 1266	10.5	12.8	24.1	13.6	0.0	1.7	76	2	Dec.	VST	Negative	1.2	0	0	
2322	F	25.2	25.3	34.7	9.5	0.0	2.0	40	5	Jan. 1931	VST	20-40 WBC; p.h.p.f.	Tr.			
2556	M	32.5	32.7	41.4	8.9	0.0	1.0	35	4	Nov.	VST	Rare WBC; p.h.p.f.	0.5	0	0	
3158	M	Son	51.5	61.5	69.1	17.6	0.0	1.8	10	1	Dec.	SPT	Rare WBC; p.h.p.f.	0.7	0	0	
3950	F	Sister	21.2	21.5	28.0	6.8	0.0	2.0	56	2	Dec.	VST	5-10 WBC; p.h.p.f.	0.5			
5094	F	20.6	22.3	27.4	6.8	0.0	1.2	17	2	Dec.	ST	Negative	0.4	0	0	
Averages and totals 7 cases	M-3 F-4	Hereditary cases—4	23.8	26.1	33.8	10.0	0.0	1.6	56	3	0.6

* All urine specimens listed above under "Last Examination of Urine" (Fall, 1930) were obtained after an overnight fast except in Case 4025, in which the urine was voided $\frac{1}{2}$ hour after lunch, and in Cases 2556, 3158 and 5094, in which 24-hour amount specimens were used.

† Carbohydrate tolerance tests were performed after an overnight fast in all instances except as follows: Case 8357, 1½ hours after breakfast; Case 8834, 1½ hours after lunch; Case 8885, 1 hour after breakfast. Blood sugar values in "Fasting" column are, therefore, not fasting values.

"TYPICAL" AND 7 CASES OF "ATYPICAL" RENAL GLYCOSURIA.

Last exam. of urine.*				Blood sugar.			Carbohydrate tolerance tests.†										Present condition.			
Fermentation test.	Benedict's test after fermentation.	Phenylhydrazin test for dextrose.	Melting point of osazone crystals, ° C.	Recorded examinations.	Highest recorded values.		Date.	Test meal.	Blood sugar values.						Date, 1930.	(Clothed) weight pounds.	Health.	Diet.		
					Fasting, gm. per 100 cc.	After a meal.			Hours after glucose.											
									Fasting.	½	1	1½	2	3½						
+	0	+	208	8	0.10 0.10	..	1921 100 gr. glucose	0.07	0.10	..	0.09	..	0.10	Dec.	160	Well	Normal.			
+	0	+	208	33	0.11 0.15	1	1921 100 gm. glucose	0.11	0.13	0.13	..	0.15	..	Dec.	166	Well	Normal.			
..	8	0.08 0.14	1	1922 C ₆₀ P ₆ F ₆	0.08	0.14	0.14	..	0.10	..	Nov.	145	Well	Normal.			
+	0	7	.. 0.13	3½	Sept.	130	Well	Normal.			
..	15	0.07 0.11	2½	Sept.	169	Well	Normal.			
+	0	+	203	13	0.04 0.09	1	Sept.	75	Well	Normal.			
+	0	+	..	11	.. 0.13	1	1927 100 gr. glucose	..	0.11	0.08	..	0.08	..	Nov.	118	Well	Normal.			
+	0	5	.. 0.13	1½	Nov.	182	Well	Normal.			
+	0	+	..	3	.. 0.09	1½	Sept.	157	Well	Normal.			
+	0	+	..	21	.. 0.12	1	Sept.	62	Well	Normal.			
+	0	+	..	20	.. 0.16	1½	Sept.	63	Well	Normal.			
+	0	+	..	6	.. 0.12	1	Dec.	172	Well	Normal.			
+	0	+	..	7	.. 0.14	1	1929 100 gr. glucose	0.07	0.11	0.10	..	0.09	..	July	94	Fairly well	Normal.			
+	0	+	..	7	.. 0.15	½	1930 100 gr. glucose	0.14	0.15	0.12	..	0.13	..	May	108	Fairly well	Normal.			
+	0	+	..	8	.. 0.14	2	1930 100 gr. glucose	0.10	0.14	0.11	..	0.14	..	May	152	Well	Normal.			
..	11	0.08 0.13															

Atypical Renal Glycosuria.

..	8	0.10	0.15	Accidental death, March, 1922.			
+	0	+	..	9	0.12	0.22	1	1923	30 gm. glucose	0.08	..	0.22	..	0.10	..	Sept.	100	Well	Normal.
..	29	0.09	0.22	1½	1921	100 gm. glucose	0.07	0.12	0.11	..	0.09	..	Sept.	111	Well	Normal.
+	0	+	..	26	0.11	0.15	½	Nov.	144	Well	Normal.
+	0	+	..	5	0.07	0.16	½	1923	C ₇₀ P ₁₀ F ₂₄	0.07	0.16	0.15	Dec.	120	Well	Normal.
..	16	..	0.21	½	Nov.	102	Well	Normal.
+	0	+	..	12	0.10	0.12	1	Sept.	107	Well	Normal.
..	15	0.10	0.18													

† In test for albumin in urine the following symbols were used: SPT = slightest possible trace; VST = very slight trace; ST = slight trace. Tests designated as SPT and VST may be regarded as normal.

§ In report of urinary sediment, WBC = white blood corpuscles, RBC = red blood corpuscles and p.h.p.f. = per high power field of microscope.

3. *Blood Sugar.* Folin's methods of blood sugar analysis were used throughout. For the most part, the method published in 1920¹⁹ was employed for the analysis of venous blood. Capillary blood sugar analyses reported in this paper were done by the micro-method of Folin and Malmros.²⁰

Presentation of Data. In Table 1 the 22 patients are divided into two groups:

1. Those with "typical" renal glycosuria, 15 in number. In the years of observation thus far since the discovery of glycosuria in these patients there has never been recorded a sugar-free specimen of urine nor an abnormal blood sugar.

2. Those whose clinical behavior is typical of renal glycosuria, but whose urine on rare occasions has been found free from sugar or whose blood sugar has been found at times to be slightly above the the value regarded as normal in this clinic; there are 7 cases in this group.

It is possible that time and more thorough study may relegate some cases from Group 1 to Group 2. Objection may be made that the division between the two groups is illogical since all 22 patients are individuals with a low renal threshold for sugar and a benign type of glycosuria. Further objection may be made that under conditions of starvation or large insulin dosage²¹ sugar-free urine might be produced in patients in Group 1. However, we feel that for the purpose of future study it is worth while to put into one distinct group 15 patients who thus far fulfill the requirements set up for the diagnosis of renal glycosuria.

I. PATIENTS WITH TYPICAL RENAL GLYCOSURIA. In Table 1a are presented the outstanding features of the case histories in this group of 15 patients. All 15 of these patients are living.

Sex. The almost equal distribution between the sexes differs from that in the group of 69 cases collected from the literature by Finley and Rabinowitch²² in which 48 were males and 21 were females.

Race. Two of the 15 patients are Hebrews.

Heredity. In 11 instances (73 per cent) a family history of glycosuria was obtained. This striking factor of heredity has been mentioned repeatedly in the literature. In our series there are 3 instances of true renal glycosuria occurring among brothers and sisters, as follows: (a) The brother of Case 4025 was considered at the Peter Bent Brigham Hospital in Boston to have renal glycosuria; (b) Cases 6708 and 6709 are sisters; (c) the brother of Case 5745 appears to have typical renal glycosuria but is not included in this series because a recent urine analysis was not available. The father of these 2 boys is said to have had diabetes "in attacks."

The great grandmother of Case 2279 was said to have died of diabetes at the age of 77 years; obviously if she had true diabetes

the disease was mild. The mother of Case 3618 is Joslin's Case 1980 and is listed as having "unclassified glycosuria." Case 4160 has a striking family background of glycosuria. Four relatives are patients of Joslin (mother, Case 1470; father, Case 3598; 2 paternal uncles, Cases 2254 and 5019). These patients and another paternal uncle, not treated here, all have glycosuria which never has been proved to be diabetic. The mother, sister and brother of Case 6252 are reported to have or to have had diabetes; the mother died in coma. One paternal uncle of Case 6314 is recorded as having diabetes. The father of Case 8885 had glycosuria which was noted after an injury.

Accordingly, none of these patients have relatives who have been observed in this clinic to have had diabetes mellitus, although the evidence from other sources, as outlined above, strongly points to this, particularly in the instance of Case 6252.

Age at Discovery of Glycosuria. The average age at which glycosuria was first discovered was 19.9 years. The earliest age at which it was noted was in Case 6708 at 4.8 years. Onset under 10 years was noted also in Cases 6709 and 4160. The onset was in 6 instances in the second, in 4 instances in the third and in 1 instance in the fourth and fifth decades. It is, indeed, striking that in 9 of the 15 cases urinary sugar was found first before the age of 20 years. Goldbloom²³ reported a case in an infant, aged 20 months, whose father also had renal glycosuria. The infant was observed only for 6 weeks, however, and the urine became sugar-free.

Duration of Glycosuria. The average length of time from the discovery of glycosuria to December, 1930, was 9.3 years, with a range from 3 to 36 years. Relatively few cases of long duration of glycosuria are recorded in the literature. Case 1 of Finley and Rabinowitch²² was studied carefully 29 years after the discovery of glycosuria, but apparently he was sugar-free for part of that time. Probably the first case reported in the American literature was that of Strouse and Beifeld.²⁴ Sugar was found in the urine of their patient on November 6, 1912. On December 11, 1930, Strouse wrote us that this man is alive and in good health. A recent urine examination showed a trace (less than 0.2 per cent) of sugar. However, the rather high blood sugar values which at times have been obtained in the study of this patient would exclude him from the group of cases which we are reporting in this paper. His glycosuria apparently is benign, however.

Symptoms. Ten of the 15 patients have never complained of polyuria, polydipsia or loss of weight. Four patients (Cases 2165, 4025, 4160, 6314) complained of polyuria, 3 (Cases 2165, 4160, 6314) of polydipsia, 2 (Cases 2279 and 4160) of loss of weight and 4 (Cases 4025, 4160, 6252, 6709) of easy fatigability or weakness. These symptoms in most cases were recorded on the history as "slight." No patient complained of polyphagia, pruritus or fur-

unculosis. Since Case 4160 was only 6 years of age the symptoms as given may not have been accurate.

Glycosuria. Of the 15 patients 13 have shown at one time or another 1 per cent or more sugar in the urine; 11 have shown at times 2 per cent or more. Case 2165 has excreted as high as 110 gm. of sugar per 24 hours. Case 2279 has excreted from 7 to 102 gm. per 24 hours. On the other hand, Cases 2768 and 4160 have recorded excretions of only 1 to 7 gm. and Case 4025, 12 to 18 gm. per 24 hours. No patient in the series has a sugar-free urine specimen listed in our records. The urine (voided before breakfast) of every patient was examined in the fall of 1930 and found to contain sugar in the amounts indicated in Table 1. The striking persistence of urinary sugar excretion (or at least, of copper-reducing substances) in Case 2279 even during fasting is shown in Table 2. Unfortunately at that time no tests were made to prove that the small amounts of reducing substances were actually dextrose.

TABLE 2.

Mr. L. C.; Case 2279; Age, 17.9 Years.

Date, 1921.	Urine.				Diet per 24 hours.				Fasting blood sugar, gm. per 100 cc.
	Volume, 24 hrs. cc.	Diabetic acid.	Sugar.		CHO, gm.	P., gm.	F., gm.	Cal.	
			Per cent.	Grams per 24 hrs.					
Jan. 28-29 . . .	1600	0	2.5	40	21	7	0	112	0.08
Jan. 29-30 . . .	3300	0	0.8	26	64	33	0	388	
Jan. 30-31 . . .	2000	0	0.9	18	36	27	0	252	
Jan. 31-Feb. 1 . . .	1400	Sl. +	0.9	13	15	5	0	80	0.07
Feb. 1-2 . . .	1450	Sl. +	0.5	7	0	0	0	0	
Feb. 2-3 . . .	1900	Sl. +	0.5	10	0	0	0	0	
Feb. 3-4 . . .	2200	0	0.3	7	0	0	0	0	0.06
Feb. 4-5 . . .	3400	0	0.2	7	0	0	0	0	
Feb. 5-6 . . .	1650	Sl. +	0.4	7	20	33	10	302	
Feb. 6-7 . . .	1600	0	0.7	11	36	46	21	517	

It will be noted from the above that the excretion of reducing substances in the urine continued despite subnormal blood sugar values. Marsh²⁵ has published similar observations made in a very complete study.

Type of Sugar. Tests for levulose and pentose were negative in all specimens of patients listed in Table 1a. Control tests with known levulose and gum arabic solutions and with normal urine were made, so that the interpretation of the results of the Seliwanoff and Tollen tests was judged by as good standards as we could devise. Despite this, we did not find these tests entirely satisfactory.

In 11 cases the sugar was precipitated by phenylhydrazin. The osazone formed was identified microscopically as that characteristic of dextrose. In 3 instances the melting point of the osazone* was found to be that characteristic of dextrosazone, and this was not altered by the addition of known dextrosazone crystals.

Blood Sugar Values. Fasting blood sugar values are available in 5 cases. The highest recorded values range from 0.04 to 0.11 gm. per 100 cc. of blood. The highest blood sugar values obtained after a meal vary from 0.09 to 0.16 gm. per 100 cc. Most of them were taken within an hour after a meal. The average highest postprandial value for the group is 0.13 gm. per 100 cc.

Carbohydrate Tolerance Curves. In 7 instances tolerance curves were made either following 100 gm. of glucose or (in Case 2768) a test meal of 2 shredded wheat biscuits and 120 cc. of milk, which contained carbohydrate, 50 gm.; protein, 10 gm.; and fat, 6 gm. The individual tests are set forth in Table 1. In general, the curve was quite flat, rising normally from the control value. In Cases 8357, 8834 and 8885 the test quantity of glucose was given 1 or 1½ hours after an ordinary meal. These particular curves show values which are somewhat greater but still within normal limits.

Evidences of Accompanying Nephritis. None of the 15 patients has at any time given evidence of the presence of nephritis. For that reason not many tests are recorded. However, Case 2165, in 1921, after 27 years of glycosuria had a phenolsulphonaphthalein excretion of 62 per cent in 2 hours, a normal blood nonprotein nitrogen value and a normal variation in the specific gravity of the urine. The phthalein excretion of Case 2279 was 90 per cent in 1921 and that of Case 4025 44 per cent in 1924.

The microscopic examination of the urinary sediment in the recent analyses (Table 1) has shown no abnormality of note in any of the 15 cases. The urine of most of the patients gave a faintly positive reaction for albumin by the very sensitive Robert and sulphosalicylic acid tests. The incidence of positive tests, however, is probably no greater than that in an average group of individuals coming for routine examination to this office.

Present Condition. The 15 patients reported in Table 1a reported in person or by letter during the last 4 months of 1930. All are in excellent health and maintaining a normal weight except Cases 8357 and 8834, whose weights are slightly subnormal. Their complaints are mild and seem unrelated to the glycosuria. All are on a normal diet. A few patients avoid straight sugar as in tea and coffee.

The effect of fasting or of low caloric diets was tried in 4 of the earlier cases. Case 2165 was on a low intake from 1894 to about 1904 without ever having a sugar-free urine. His condition im-

* We are greatly indebted to Dr. C. F. Bailey of the Department of Organic Chemistry of Harvard University for certain of the melting-point determinations.

proved greatly when he began experimenting with higher diets. He now observes no dietary restrictions and is in good health. In 1921 Case 2279 (referred to above) was kept under observation in the hospital for 14 days and food was withheld entirely for 4 days. His urine was never sugar-free. The urine of Case 2768 did not become sugar-free when she was kept for 8 days on a diet containing less than 1200 calories. Diets containing from 500 to 800 calories a day failed to make the urine of Case 4160 (then 6 years of age) free from sugar, despite fasting blood sugars of 0.03 and 0.04 gm. per 100 cc. and blood sugars of 0.07 and 0.09 gm. per 100 cc. 1 hour after a meal. During this period the urinary sugar varied from 0.5 to 1.8 per cent per 24 hours.

The Effect of Insulin. Case 4025 received insulin for 6 days in doses of from 5 to 30 units a day. Despite a low caloric diet (for 4 days under 1250 calories per day) the urinary sugar was unaffected. Cases 6708 and 6709 (then 5.5 and 6.4 years of age, respectively) received insulin for 6 days in doses of 10 to 20 units a day without affecting the urinary sugar output. This lack of effect has been frequently commented upon^{26,27} but as Powelson and Wilder²¹ point out, it is possible that if very large doses of insulin had been used sugar-free urine might have been secured through extreme lowering of the blood sugar.

II. PATIENTS WITH ATYPICAL RENAL GLYCOSURIA. In Table 1b are shown the data of 7 other patients with undoubted benign glycosuria. These patients have a low renal threshold for sugar and excrete sugar in the urine almost constantly. However, they have had occasional sugar-free specimens and Cases 1612, 2322 and 3959 have had occasional abnormal blood sugar values. (It is only fair to state that the value of 0.22 gm. per 100 cc. in the case of No. 2322 is the only abnormal value in 29 determinations. Since her tolerance curve is so flat in shape (Table 1b) it is possible that the value of 0.22 was a laboratory error.)

Of these 7 patients 1, Case 1266, quite well and strong at the time, died in March, 1922, in a coasting accident. His sister, Case 1612, is alive and very well today, living on an unrestricted diet.

Three of the 7 patients are males and 4 are females. Four gave a family history of glycosuria. The mother of Cases 1266 and 1612 has glycosuria; 1 maternal aunt and 2 paternal great-aunts are said to have had diabetes mellitus. The son of Case 3158 has a condition much similar to that of his father, except that his urine does not so regularly contain sugar and he has had very slightly abnormal blood sugar values. The sister of Case 3959 is said to have diabetes.

The age of discovery of glycosuria varied from 5.4 to 51.5 years. The average known duration of glycosuria is 10 years and varies from 6.8 to 17.6 years.

Symptoms have been few. Case 1266 when first seen complained of polyuria, polydipsia and polyphagia; he was only 7 years of age at the time, however, and later was quite well and strong. Case 1612 complained of polydipsia, Case 5094, of polyphagia and easy fatigability, and Case 2322, of easy fatigability.

Urinary sugar has varied from 0 to 2 per cent. In Cases 1266 and 1612, in whom a great many tests were done, the 24-hour excretion of sugar varied from 0 to 14 and 0 to 12 gm., respectively. At the last examination (in the fall of 1930 in every case except Case 1266) all showed sugar in the urine and in 4 instances this was proved to be dextrose.

The values for the blood sugar obtained fasting, after a meal, and during a tolerance test are given in the table and need no further comment.

The 6 living patients are at the present time in good health, have a normal weight and are observing no dietary restrictions.

The effect of fasting was tried in 2 patients of this group. Case 1266 when starved in 1917 became sugar-free. His fasting blood sugar then was 0.07 gm. per 100 cc. On a diet containing 400 calories a day (carbohydrate, 15 gm.; protein, 30 gm.; fat, 24 gm.) sugar reappeared in the urine. Case 2322 became sugar-free on 80 calories a day (carbohydrate, 15 gm.; protein, 5 gm.; and fat, 0) and diacetic acid appeared in the urine. Her fasting blood sugar was at the time 0.06 gm. per 100 cc.

Discussion. Of more interest than the presentation of cases of renal glycosuria is a consideration of the nature of the disorder. The early experiments of von Mering²⁸ showed that the subcutaneous injection of phloridzin causes glycosuria without hyperglycemia. Zuntz²⁹ showed further that this glycosuria most likely is due to local change in the kidney. He found that the injection of phloridzin directly into the renal artery of one side causes the immediate excretion of sugar from the kidney supplied by that artery. Not until later does sugar appear in the urine from the opposite kidney. The knowledge of these experiments naturally focussed attention upon the kidney in the spontaneous normoglycemic glycosuria in man.

In fact, the earliest reported cases of renal glycosuria had antecedent or concomitant nephritis. It was maintained by Luthje³⁰ and others that such association was essential for the diagnosis of renal diabetes. Bönniger³¹ and von Noorden³² insisted, however, that the one abnormality had nothing to do with the other. In the recent literature writers have taken pains to state the renal function of reported cases. There has been general agreement that this is normal.^{22, 25, 33} There is nothing in our data to suggest that in the cases of renal glycosuria there is accompanying nephritis. Mild albuminuria is probably no more frequent than in the average individual coming for routine examination. We have been unable

to find in the literature an account of an autopsy on a renal glycosuric. There is nothing known of the morbid anatomy of the disease. Since the exact mechanism of the production of glycosuria by means of phloridzin is far from clear,³⁴ studies of this condition have been of limited value in the understanding of renal glycosuria.

In renal glycosuria in man everything seems to point to normal functioning of the pancreas. The blood sugar is normal, insulin administration has little or no effect upon the glycosuria^{26, 27} and metabolism and respiratory quotient determinations have shown no impairment of the body's ability to store and to use carbohydrate.¹⁴ Ketosis develops when the patient fasts rather than when he overeats.³⁵ It may develop under postoperative conditions³⁶ in the renal glycosuric as in the normal individual.

This lack of diabetic symptomatology, the lack of progression of the disease and the obvious benignity of the condition set it off from true diabetes mellitus. On the other hand, the occurrence in the same family group of an individual with diabetes mellitus, of another with renal glycosuria and perhaps others with transient or cyclic glycosuria is enough to make one wonder as to the possible association of the various types. There are reports too of the occurrence in the same individual of true diabetes and a low renal threshold.^{21, 37} Despite this, Hjärne's³ study of glycosuric families led him to believe that orthoglycemic glycosuria and diabetes mellitus probably have a different origin and that no transition occurs between the two. He regarded their occurrence in the same families as a possible chance coincidence.

Geyelin³⁸ states that "observation of patients with this condition (of renal glycosuria) over prolonged periods shows that a certain number develop true diabetes mellitus," but quotes no actual cases. Umber and Rosenberg³⁹ believe that they have seen cases progress from glycosuria innocens to diabetes mellitus, but as Hjärne³ points out, 1 of these patients had on first admission a fasting blood sugar that was distinctly abnormal (0.156 gm. per 100 cc.). Gottschalk and Springborn⁴⁰ take for granted that patients with harmless glycosuria of the renal type may later progress to true diabetes mellitus, often with persistence, however, of the "renal" element. Their first patient, however, at the time of first observation had distinctly abnormal blood sugar values. This change from true renal glycosuria to true diabetes mellitus has not occurred in any of the cases seen in this clinic. Our experience agrees with that of Faber,⁴¹ Hjärne³ and Holst.⁴²

In a condition in which the diagnosis depends entirely on laboratory findings it is difficult to ascertain whether or not the disorder is congenital. Our records certainly suggest that at least in some instances renal glycosuria is *not* congenital. In addition to the data given in Table 1 we know further that the children of Case 2165

had sugar-free urine a year ago but now have glycosuria. On the other hand, the condition usually appears early in life. In 9 of our 15 typical cases glycosuria was discovered before the age of 20 years. In several of our patients the history is given that, following the initial discovery of urinary sugar, dieting at first produced a sugar-free urine. Then perhaps for weeks or months sugar appeared in the urine intermittently. Finally when first seen in the office or hospital these same patients were found to have constant glycosuria which *had* persisted to date. This type of history argues for a gradual acquisition of the lowered renal threshold, although undoubtedly in most cases due to an inherited tendency.

True renal glycosuria is presumably a permanent condition lasting from the time of onset until the end of life. Whether it can ever be a temporary state is questionable. Faber⁴¹ believes that in the same individual the renal threshold for sugar is the same throughout life. Certainly, however, as he agrees, it is lowered during pregnancy and upon the administration of phloridzin. It is probably also lowered at the onset of the spontaneously arising condition of renal glycosuria. Whether this may at times be due to toxic injury to the kidney, as during infections, is not known. We know that following pregnancy and following the cessation of the effect of phloridzin the normal threshold is regained. It seems reasonable to suppose that this might occur in the case of renal glycosuria. Fitz⁸ mentions such a case. No such case has been seen in this clinic. In our group of discarded cases there are a few which seem to have shown this transient character, but in every instance the diagnosis was made originally after only brief observation because past history of glycosuria seemed at the time to warrant it.

Although there may be some unknown extrarenal factor in their causation, the different types of benign glycosuria seem at least partly explainable on the existence of different levels of the renal threshold for sugar. At one extreme are those cases which we choose to classify as instances of "typical" renal glycosuria. These individuals have sugar in the urine at absolutely normal or even subnormal levels of blood sugar. Then there are individuals who show urinary sugar only when, as after a meal, the blood sugar rises above 0.11, 0.12 and 0.13 gm. per 100 cc. The glycosuria of such individuals corresponds to the alimentary glycosuria or "cyclic" renal glycosuria of others⁴² and have been designated as "unclassified" cases by Dr. Joslin. The glycosuria is of the "renal" type, to be sure, and it is undoubtedly this latter condition which Folin and Berglund⁴³ refer to as being so common. We believe that constant glycosuria irrespective of blood sugar is a rare condition.

It is self-evident that the practical danger in making the diagnosis of renal glycosuria lies in the confusion of this condition with that of "potential" or mild diabetes mellitus which without adequate

treatment may increase in severity. Special care is necessary in the diagnosis of the glycosuria of pregnancy which is by no means always of the benign "renal" type which disappears after the termination of the pregnancy. For the diagnosis of renal glycosuria, therefore, we believe that observation over a period of years is necessary. When the diagnosis is tentatively made the patient should be carefully followed. Tests of blood and urine should be made every 3 months for the first year and every 6 or 12 months thereafter.

Summary. 1. A definition of renal glycosuria is stated. Only 15 cases in a study of 9000 cases of glycosuria were found which fulfilled the requirements as outlined. In addition, 7 cases were found which are considered typical of renal glycosuria except for an occasional sugar-free urine specimen or an exceptional blood sugar value above the limit of normal set by this clinic.

2. Two cases of chronic ("essential") pentosuria were discovered among the patients with supposed renal glycosuria.

3. No case in the group has recognizably progressed toward diabetes mellitus despite the fact that of the 15 "typical" cases, 5 have had glycosuria for over 10 years and 1 for over 36 years.

4. In 13 of the 15 cases glycosuria was first noted before the age of 30 years. In 3 cases onset was noted before the age of 10 years and in 9 cases before the age of 20 years.

5. The history of glycosuria in the relatives of the patient was obtained in 11 of the 15 cases.

6. No evidence of nephritis was found in any of the patients.

7. Because of its rarity care should be made in making the final diagnosis of this type of glycosuria.

Case Report. Because of the very long duration of glycosuria, Case 2165 deserves special mention. This patient, Mr. C. M. D., born April 21, 1884, was always well until September, 1893, when, at the age of 9½ years, he began to experience occasional attacks of asthma particularly in the winter after upper respiratory infections. Sugar was first noted in the urine in the spring of 1894. The amount is said at that time to have been as great as 2 to 4 and even 10 per cent of sugar. For 10 years he was kept on a strict dietary régime. However, despite a low carbohydrate intake, urine analyses every month or two showed large amounts of sugar, varying from 1 to over 3 per cent. Figures at hand indicate that the sugar excreted per 24 hours varied from 19 to 105 gm. Gradually he began to disregard precautions of diet. In college (1904 to 1908) he ate a full diet except for the omission of sugar and sweet desserts and has continued to do so until the present time.

He consulted Dr. Joslin in April, 1921. At that time he was 38 years of age, was 5 feet 10 inches tall, and weighed 140½ pounds (without clothing). His only complaint was that of lack of energy. He had had slight polyuria and polydipsia at times. Physical examination showed no abnormalities. The blood pressure was 130 systolic and 80 diastolic. A typical urine analysis is included under the date of April 20, 1921, in Table 3 below.

TABLE 3.—URINALYSES FROM 1899 TO 1930.

Mr. C. M. D.; Case 2165.

Date.	24-hour amount, cc.	Specific gravity.	Albumin.	Diacetic acid.	Sugar.	
					Per cent.	Grams in 24 hrs.
Jan. 24, 1899 . . .	1920	1.037	—	0	3.0	58
Sept. 11, 1899 . . .	4000	1.020	—	0	1.7	68
Mar. 13, 1900 . . .	2820	1.027	—	0	2.6	73
Sept. 22, 1900 . . .	3000	1.026	—	0	3.5	105
Mar. 30, 1901 . . .	1440	1.042	Trace	0	2.5	36
Oct. 4, 1902 . . .	2940	1.023	—	0	1.0	29
Apr. 4, 1903 . . .	1600	1.036	—	0	2.0	32
Sept. 8, 1904 . . .	1800	1.050	—	0	0.9	16
Sept. 20, 1904 . . .	3360	1.018	—	0	2.0	67
Apr. 9, 1906 . . .	2800	1.030	—	0	3.0	84
Sept. 12, 1906 . . .	2900	1.026	—	0	2.0	58
Apr. 20, 1921	S. p. t.	0	2.5	
Sept. 9, 1921 . . .	2340	1.030	—	—	4.7	110
Oct. 8, 1921 . . .	1700	1.043	—	—	5.6	95
Jan. 8, 1922 . . .	2100	1.032	—	—	4.0	84
June 15, 1925 . . .	1620	1.030	—	+	4.2	68
Oct. 26, 1925 . . .	1980	1.028	—	0	3.3	65
July 23, 1928	1.016	0	—	2.0	
Sept. 22, 1930 . . .	1860	...	0	0	4.3	80

In the urine there was no diacetic acid, only a slightest possible trace of albumin and no abnormalities in the sediment. The nonprotein nitrogen of the blood was 34 mg. per 100 cc., despite a moderately high protein diet (85 to 113 gm. of protein a day). The phenolsulphonaphthalein excretion was 62 per cent in 2 hours. A "2-hour renal" test showed a variation in specific gravity from 1022 to 1042. The fasting blood sugar was 0.10 gm. per 100 cc. on one occasion and 0.07 gm. per 100 cc. on another. The tolerance curve done after a test meal is included in Table 1a.

Since 1921 his course has been uneventful. Periodic urine examinations have invariably shown sugar (Table 3). A note from him in November, 1930, states that his health is excellent although he has not as much energy as formerly. He was ill with dengue fever in Cuba for 3 months in 1925. His physical examination* in September, 1930, was normal. His weight was 159½ pounds and his blood pressure was 128 systolic and 85 diastolic. No albumin was found in his urine on September 22, 1930. The blood sugar was 0.09 gm. per 100 cc. He has 4 healthy children. The 2 oldest of these, Elizabeth, 13½, and Evans, 9½, were found in October, 1930, to have 0.8 per cent and 0.6 per cent urinary sugar, respectively. Both had a normal blood sugar. Both had been examined 1 year before and no urinary sugar found. For details as to the identification of urinary sugar see Table 1a.

The points elicited by this study are summarized on the preceding page.

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* Data kindly supplied by Dr. Matthew Griswold, Jr.

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CHRONIC ESSENTIAL PENTOSURIA:

A REPORT OF THREE CASES.

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ALTHOUGH alimentary pentosuria is said to occur rather frequently after the ingestion of large amounts of fruits, chronic "essential" pentosuria is usually regarded as a rare condition.¹ In the course of a recent study described in an accompanying article² two such cases were discovered among a group of patients with supposed renal glycosuria. Their discovery emphasizes the fact that unless the type of urinary sugar is determined, chronic pentosuria may be easily mistaken for renal glycosuria.³ These 2 cases, and a third case more recently discovered (among the group of patients with "unclassified" glycosuria), represent the only recognized instances of chronic pentosuria among 9000 consecutive cases of mellituria seen by Dr. Elliott P. Joslin and associates.

In the identification of the type of sugar excreted in the urine the methods used were those described in the preceding article,² namely, Seliwanoff's reaction for levulose and Tollens' phloroglucinol test for pentose,⁴ the fermentation test and the phenylhydrazin test.⁵ In performing the fermentation test the urine was incubated in a saccharometer in the presence of bakers' yeast for 12 to 24 hours at 25° to 30° C. After allowing time for fermentation the Benedict test for sugar was repeated to ascertain whether or not the reducing substances had disappeared. The osazones formed during the phenylhydrazin test were identified under the microscope, and after recrystallization the melting point of the crystals was determined.*

* Dr. C. F. Bailey of the Department of Organic Chemistry of Harvard University kindly made the melting point determinations.

Case Reports.—CASE 1. Mr. L. L., No. 1473, a Jewish dry-goods merchant, consulted Dr. Joslin first on January 14, 1918, at the age of 28½ years. Sugar had been found in his urine at each of several examinations performed since its discovery in February, 1917. He had been regarded as having diabetes mellitus. He had no complaints other than glycosuria. His family history and past history were irrelevant. Physical examination revealed no abnormalities. He remained in the New England Deaconess Hospital from January 14 to 25, 1918. During that stay, urinary sugar was constantly present in the 24-hour collections of urine, in amounts varying from 0.1 to 0.4 per cent (1 to 3 gm. per 24 hours). As may be noted in Table 1 below, urinary sugar was found even during 2 days of complete fasting.

TABLE 1.—MR. L. L., NO. 1473, PERSISTENCE OF MELLITURIA DESPITE FASTING.

Date, 1918.	Urine.			Diet per 24 hrs.				Blood sugar, gm. per 100 cc. ,
	Dia- cetic acid.	Sugar.		CHO, gm.	P. gm.	F. gm.	Cals	
		Per cent.	Gm. in 24 hrs.					
January 15-16	0	0.2	2	87	20	6	482	0.12 (? time).
16-17	0	0.2	2	87	20	6	482	
17-18	0	0.1	1	41	13	3	243	
18-19	0	0.3	2	0	0	0	0	0.10 (fasting).
19-20	0	0.2	2	0	0	0	0	
20-21	0	0.2	3	33	65	55	887	
21-22	0	0.1	2	33	65	55	887	0.11(after eating).

From 1918 to date he has remained in good health and has had a normal weight. He has not restricted his diet except for the avoidance of actual sugar, as in coffee. Repeated examinations have invariably shown urinary sugar in amounts varying from 0.1 to 1.5 per cent.

On December 9, 1930, routine examination of urine passed before breakfast gave the following findings: Specific gravity, 1.017; acid reaction; very slight trace of albumin; no diacetic acid; 0.4 per cent sugar; no blood, pus, or casts in the sediment.

Special tests of the urinary sugar gave a negative reaction for levulose and a positive test for pentose. Incubation at 25° to 30° C. with bakers' yeast for 12 hours yielded no gas and the urine reduced Benedict's solution afterward. The phenylhydrazin test yielded crystals microscopically characteristic of pentosazone. After recrystallization, the melting point of the crystals was 157° to 159° C.

CASE 2.—Mr. C. L. S., No. 6760, Jewish, college student, was first seen by Dr. Joslin on March 27, 1928, at the age of 20 years. Both grandmothers are said to have diabetes. Sugar had been found in the patient's urine when he was 12 years old and he had been treated as a mild diabetic since then. It was stated, that following dietary treatment in 1920 the urine became sugar-free for a time. A positive test was obtained in December, 1921, however, and at almost every examination since then.

When first seen by Dr. Joslin, the patient complained of chronic headaches and lassitude. His physical examination, however, showed nothing abnormal. Examination of the urine showed a slight possible trace of albumin and 0.4 per cent sugar. His blood sugar was 0.11 gm. per 100 cc. 1 hour after supper. On April 2, 1928, several urinary specimens were examined with the following results:

Time.	Specific gravity.	Diabetic acid.	Sugar per cent.
9.30 A.M. (fasting)	1.019	0	0.3
11.30 A.M. (1 hr. after breakfast)	1.018	0	0.3
1.00 P.M. (before lunch)	1.025	0	0.4
2.30 P.M. (1 hr. after lunch)	1.015	0	0.2
4.00 P.M.	1.019	0	0.3
6.30 P.M. (before supper)	1.011	0	0.2
8.00 P.M. (1 hr. after supper)	1.016	0	0.2

On June 28, 1928, urine voided 2 hours after lunch gave the only negative test for sugar that is listed among 20 entries on the record in this Clinic. Blood sugar at this time was 0.09 gm. per 100 cc. Subsequent examinations of the urine and blood (taken simultaneously) are tabulated below.

TABLE 2.—MR. C. S. L., No. 6760, URINE AND BLOOD EXAMINATIONS.

Date.	Time.	Specific gravity.	Sugar per cent.	Blood sugar, gm. 100 cc.
August 14, 1928	1 hr. after lunch	1.035	0.6	0.10
October 30, 1928	1 hr. after light lunch	1.014	0.2	0.10
May 25, 1929	5 hrs. after lunch	1.030	0.7	0.09
October 3, 1929	3½ hrs. after lunch	1.034	0.8	0.09
December 8, 1930	Fasting	1.012	0.3	
December 29, 1930	24 hr. amount	1.024	0.6	

By the sensitive Robert's test a very slight trace of albumin has usually been found in the urine. The urinary sediment always has been absolutely normal, and the blood pressure normal. For the last 2 years the patient has felt very well and has had a normal weight. He observes no dietary restrictions.

On December 29, 1930, special examination of the type of urinary sugar as in Case No. 1473, gave a negative reaction for levulose, a positive test for pentose, no fermentation with bakers' yeast, and, with phenylhydrazin, crystals characteristic of pentosazone. After two recrystallizations, the melting point of the crystals was 160° C.

Mixing of the pentosazone crystals from the 2 cases produced no alteration in the previously determined melting point.

CASE 3.—H. T., No. 7995, Jewish, was first brought for examination on July 2, 1929, at the age of 7 years. Four years previously a small amount of sugar had been found in his urine. An uncle and an aunt of his father were known to have diabetes mellitus (Cases 2864 and 2865, respectively); otherwise his family history was negative. He had had pneumonia (when 2 years of age), jaundice, tonsillitis and measles prior to our first examination. Physical examination revealed no findings of note other than palpable cervical and axillary lymph nodes, a systolic heart murmur and a palpable liver. The routine blood Wassermann test was negative. He was first treated at the New England Deaconess Hospital from July 2 to 10, 1929. Only one specimen was free from sugar. He was brought for observation again in July, 1931, with the report that he had been feeling well and for 2 years had lived on a free diet.

Analyses of urine and blood are summarized in Table 3, page 830.

On July 29, 1931, he was given 40 gm. of dextrose by mouth and the following values for urine and blood sugar noted:

	Urine sugar, per cent.	Blood sugar,* gm. per 100 cc.
After ½ hour	0.5	
After 1 hour	0.4	0.12
After 2 hours	0.4	0.12

* Analysis by the micro-method of Folin and Malmros for capillary blood.

TABLE 3.—H. T., No. 7995, URINE AND BLOOD EXAMINATIONS.

Date.	Urine.			Diet per 24 hrs.				Blood sugar, gm. per 100 cc.
	Diace- tic acid.	Sugar.		CHO, gm.	P. gm.	F. gm.	Cals.	
		Per cent.	Gm. in 24 hrs.					
1929.								
July 2-3	0	0.5	0.10 1½ hr. after supper
3-4	0	0.2	2	106	48	79	1327	
4-5†	0	0.2	3	106	48	79	1327	
5-6	0	0.3	3	123	19	34	874	
6-7	0	0.4	2	103	32	52	1008	
7-8	0	0.3	2	149	36	58	1262	0.09 1 hr. after lunch
8-9	0	0.2	1	201	35	55	1409	0.08 ½ hr. after lunch
9-10	0	trace	..	House	diet	with	sugar	0.09 1 hr. after lunch
								0.06½ hr. after supper
								0.06 1 hr. after supper
								0.06 ½ hr. after breakfast
								0.08 1 hr. after breakfast
1931.								
July 27-28	0	0.4	..	House	diet	with	sugar	0.09 1 hr. after supper
								0.08 2 hrs. after supper
28-29	0	0.3	..	House	diet	with	sugar	0.08 fasting
								0.15* 11.30 A.M.

* This blood sugar analysis was done by the micro-method of Folin and Malmros on capillary blood.

† Tonsillectomy, July 5th.

On August 28, 1931, it was found that the urine gave a negative reaction for levulose, a positive test for pentose, and no fermentation with bakers' yeast. Subsequently through the courtesy of Professor Harry Trimble it has been established that the phenylhydrazin test yields crystals which resemble microscopically those of pentosazone. After recrystallization, the melting point of the crystals was 154° C.

Comment. In 1892 Salkowski and Jastrowitz⁶ reported the discovery of pentose in the urine of a morphin addict. Since then isolated reports of cases have appeared, but in 1926 Rabinowitch¹ stated that there were less than 50 cases in the literature. Margolis,⁷ in 1929, reviewed 78 collected cases. The clinical features of the condition have been discussed by these authors and by Garrod⁸ and Cammidge and Howard.⁹ It is recognized to be an asymptomatic, harmless, metabolic "error" which not infrequently occurs in several members of the same family. Published cases have shown a particular tendency for occurrence in males and in members of the Jewish race.⁸ The amount of sugar excreted is usually small (less than 1 per cent) and is independent of the diet. Therapeutic measures are unnecessary.

Fischer and Reiner¹⁰ found that after the ingestion of xylose by pentosuric children the excretion of pentose in the urine was only

slightly greater than in the normal controls. Blood sugar curves following the giving of dextrose were normal. Dextrose ingestion did not increase the amount of urinary pentose. They found that pentose tolerance curves (blood sugar) were the same in pentosuric as in normal children. These curves differed from the normal dextrose tolerance curves in that the rise came more slowly and was longer sustained. There was no increase in the nonfermentable reducing substances in the blood of the children with pentosuria.

The type of pentose excreted has been the subject of considerable discussion. In 1900 Neuberg¹¹ reported the isolation of d-l-arabinose in the urine of a patient in whom Salkowski had recognized the pentosuria. Later work, however, particularly by Levene and La Forge¹² and Greenwald,¹³ seems to indicate that the sugar is most often d-xyloketose. Our studies do not warrant a statement as to the exact type of pentose in our 3 cases.

No connection between pentosuria and diabetes mellitus has ever been demonstrated. It is obviously very important, therefore, to recognize such cases in order to reassure the patient, to prevent unnecessary treatment and to enable the granting of life insurance, if desired. Furthermore, as in 2 of the 3 cases reported in this paper, chronic pentosuria may easily be mistaken for renal glycosuria unless in all instances of continuous benign mellituria attempts are made to identify the type of sugar which is being excreted.

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THE THERAPEUTIC EFFECT OF HEMOLYSIS, ESPECIALLY IN THE ANEMIAS.

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DESTRUCTION of red cells is constantly taking place. The rate or velocity is of sufficient proportions to qualify it as a major function comparable to respiration. Earlier calculations based on pigment (mainly bile) excretion placed it at a billion per minute¹ and the life cycle of the red blood cell at 15 days.²

Recent work by Whipple and associates³ indicates that biliary pigment may have other sources than blood hemoglobin and, therefore, such a method of calculation is probably erroneous. From their observations, also confirmed from other points of view, they calculate the life cycle of the red blood cell to be, under certain conditions, more than 100 days. Even on this reduced calculation the rate of red cell destruction amounts to several billion per day. These figures are impressive and it is strange that the process has not had more study. It is of particular importance in its bearing on blood regeneration and the development and maintenance of immunity.

Red cell destruction is considered to be a function of the reticulo-endothelial system. While this system is widely distributed, it is concentrated more especially in the lymph nodes, omentum, spleen, and liver. The bone marrow is also a prominent depository of this system but here the fetal function of blood production predominates. Aschoff,⁴ who segregated and named the reticulo-endothelial system, says, "the function of blood destruction under physiologic conditions occupies a much more prominent position."

This function of blood destruction lags during fetal life and a newborn baby has an abnormally high red count, sometimes as high as 8 or 9 million.⁵ After birth, hemolysis takes place and a hemogenous icterus often appears with the count falling to normal levels. A simple and direct explanation of this whole phenomenon is that the circulatory changes activate the abdominal portion of the reticulo-endothelial system. This function of regulating blood concentration is thus seen to be a very early one in our independent existence. In this thesis I wish to enlarge on this function of blood destruction in relation to blood reproduction. Evidence has now accumulated that hemolysis stimulates new blood formation in conditions of anemia.

Reticulin is the name given to an hemolytic enzyme extracted in 70 per cent alcohol from the omentum of the pig.* It has been extracted from other organs. Alcoholic extracts of tissues are commonly hemolytic (Wells).⁶ It is standardized in hemolytic action by titrating with a 2 per cent suspension of red cells. Human,

* For details of preparation the author should be consulted directly. ED. NOTE.

sheep, or pig cells serve equally well. That amount of extract required to hemolyze 1 cc. of a 2 per cent suspension of red cells at 37° C. in 18 hours has been taken as a unit. The resistance of the red cells is determined by titration with a standard or master extract. Three years' experience with the same extracts has shown this method of assay fairly constant and reliable. In alcoholic solution there is no appreciable deterioration of the potency of the extract. It does deteriorate, however, in watery solution. It withstands a temperature of 100° but its action is slowly destroyed by boiling in water. Calcium chlorid does not suspend its hemolytic action, thereby disqualifying it as a soap. It is not protein.

This substance has been in clinical use for more than 3 years. Originally it was applied in malignant conditions with palliative effects and it was the improvement in the blood picture of these patients that caused its use to be extended to other conditions. A case of pernicious anemia in relapse, who before had required 3 months to regenerate a normal blood on liver feeding, on biweekly injections of reticulin the blood count and hemoglobin returned to normal levels in a manner similar to the response with liver:

TABLE 1.—RESPONSE OF A CASE OF PERNICIOUS ANEMIA IN RELAPSE.
LIVER RESPONSE.

	Red cells.	Hemoglobin (Sahli).	Leukocytes.
May 8, 1928	1,300,000	37	2800
June 1, 1928	2,420,000	80	3800
July 3, 1928	4,230,000	90	7200
August 1, 1928	4,560,000	95	6800

RETICULIN RESPONSE.

	Red cells.	Hemoglobin (Sahli).	Leukocytes.
March 8, 1929	3,680,000	85	2000
March 24, 1929	4,880,000	100	4800
<i>Second Trial.</i>			
September 26, 1929	3,640,000	90	5400
October 21, 1929	4,420,000	105	8000

This specific effect has been confirmed in 2 more cases of pernicious anemia. In 2 other cases who rebelled against liver and in whom transfusions became necessary, reticulin therapy alone maintained the blood at normal levels. The conclusion, then, is that in reticulin we have a remedy that may be capable of stimulating the regenerative function equal if not superior to liver feeding. An analysis of previous experimental work together with my own investigations indicates that the essential action is hemolysis and the active principle is possibly the same in both instances.

It is entirely logical to predicate blood formation on blood destruction. Duesberg⁸ has advanced this view as the explanation of erythropoiesis in pernicious anemia. He considers the liberated hemoglobin which is in turn changed to methemoglobin as the essential factor. Before him, McMaster and Haessler⁹ found that injection

of hemoglobin stimulates the bone marrow very markedly in dogs rendered anemic by bleeding. Minot and associates,¹⁰ in searching for the active principle in liver responsible for new blood production, found it was extracted in 70 per cent alcohol. They, likewise, frequently observed a drop in red count during the first 4 or 5 days of its administration indicating, "either an increase in the volume of fluid at the point of removal or a destruction of red blood cells." Extraction of several stomach and liver preparations now being used as antianemic therapy has yielded an abundance of reticulin as demonstrated by the titration method. Fetal calves liver¹¹ has yielded the richest extract of any, titrating 256 units to the cc. Thus these antianemic preparations correspond to reticulin in process of extraction and clinical response.

In some severe secondary anemias, reticulin has not been effective until iron was added. This is as reported by investigators with liver extract.¹² Apparently the liberated hemoglobin in these types is not of sufficient concentration or proper nature to stimulate the bone marrow. The pernicious anemia red cell on the other hand has a relatively rich supply of hemoglobin.

TABLE 2.—EFFECT OF RETICULIN IN SECONDARY ANEMIA FROM STOMACH ULCER. (RETICULIN 50 UNITS BIWEEKLY.)

	Red count (millions).	Hemoglobin (Dare).	Leukocytes.
April 6	3.5	54	7500
April 13	3.43	55	9000
April 20	4.09	59	7700
April 27	3.78	58	7500
(Iron added, ferrous carbonate, 30 gr. p. d.)			
May 1	3.98	59	7500
May 8	3.85	60	7250
May 15	4.18	64	7200
May 22	4.57	68	7000
May 29	4.91	70	7200

In the normal person reticulin does not produce a leukocytosis. This corresponds to the action on the red cell. In pathologic conditions the white cell increase is sometimes very striking. In a case of lobar pneumonia the count rose from 30,000 to 134,000 with 94 per cent neutrophils following 2 injections of reticulin. In a subacute case of agranulocytic angina the white count rose from 1000 to 14,000, of which 84 per cent were neutrophils, with 2 injections of reticulin. On three subsequent tests a rise of leukocytes followed reticulin therapy in this case.*

Case Report. Carcinoma of prostate in a man, aged 84 years, post-operative, with perineal and superpubic fistulæ. Reticulin 64 units biweekly.

There was a corresponding improvement in the clinical condition and the fistulæ healed promptly. The leukocytic increase is thus seen to vary as to type in different conditions and usually fluctuates considerably.

* This highly interesting case will be reported in detail by Dr. Andrew Bonthius.

TABLE 3.—EFFECT OF RETICULIN IN CARCINOMA.

Date.	Red count, mill'ns	Hb.	Leuk.	Lymph.	Neutro	Large mono. and trans.	Eosin.	Baso.
December 22, 1930	2.37	47.4	9,250	22	71	10	1	
Reticulin commenced:								
December 24, 1930	2.53	47.4	19,200	37	53	7	..	3
December 27, 1930	2.18	50.0	17,750	32	58	5	3	2
January 10, 1931	2.95	56.2	9,000	40	59	1		

The immediate effect of hemolysis is to liberate hemoglobin. The pyrrol nucleus of the bile pigment, bilirubin, is derived in part from this hemoglobin. The residue or protein fraction (globin) must go to augment plasma protein. Kerr, Herwitz, and Whipple¹³ in performing plasma depletion experiments observed a marked hemolysis in the course of plasma regeneration. In the clinical use of reticulin there is evidence of an increase of lymph. A lymphatic edema has been observed in arthritis cases where there was immobilization of the legs. There is an increased discharge of serous fluid from open wounds following its administration. In malignant cases, with invasion of lymphatic glands, an extreme lymphatic edema distal to the blockage very promptly appeared in numerous instances. These plasma proteins probably participate in antibody formation and, therefore, they become a most important subject for study.¹⁴

Clinical evidence indicates a stepping up of immunity by this form of therapy.

Case Report. A patient experienced successive crops of boils on the neck for a period of more than 2 months. Hot dressings and stock vaccine therapy were used with slight benefit. A reddened tender area appeared on the back of the hand at the level of the coat sleeve. A similar lesion appeared on the side of the neck where the collar rubbed. Reticulin, 64 units, was given and the patient 8 hours later experienced a mild chill. Next day an edema in the form of a wheal had appeared about both lesions and the color changed to a light brown. This was followed by two or three points of necrosis in the center of the wheal and copious suppuration then set in. Healing was complete in 10 days.

This reaction at the location of infection corresponds to the description of Arthus¹⁵ phenomenon which is considered an immunity reaction or a local reaction to antigen in a sensitized animal. The hemolysis by reticulin apparently liberated additional immune substances. Kyes¹⁶ and Cary¹⁷ have observed antibody production to be most abundant where hemolysis is taking place. Portis¹⁸ has observed a severe drop in antibody production in rabbits following the removal of the omentum. There is, moreover, abundant experimental evidence to indicate that the reticulo-endothelial system is active in the production of immunity.¹⁹ In connection with the case cited, Klinge²⁰ was able to retard the appearance of the Arthus

phenomenon for 48 hours by first blocking the reticulo-endothelial system with injections of trypan blue in the sensitized animal.

Other substances hemolytic in action have been used therapeutically, snake venom²¹ and lead for example. Their extensive use, however, has been restricted by their toxicity. Malarial inoculations should be considered in this category. Hemolysis rather than the febrile reaction may be the essential factor here.

Summary. 1. An alcoholic extract of the omentum and certain other organs yields a nonspecific hemolytic enzyme which has been given the name "Reticulin."

2. This extract is standardized by titration with a 2 per cent suspension of red blood cells.

3. It is administered hypodermically after evaporating the alcohol and substituting sterile water.

4. No serious toxic effects have been observed.

5. It stimulates the regeneration of both the cellular and non-cellular elements of the blood under certain conditions.

6. This hemolytic therapy heightens the immunologic response and increases the sensitivity of the host to bacterial protein (allergy).

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DIAPHRAGMATIC TIC RELIEVED BY SECTION OF PHRENIC NERVES.

REPORT OF TWO CASES.

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VARIED and often bizarre disturbances of the respiratory rhythm occurring as complications of epidemic encephalitis have been reported by many observers. The 2 cases to be described are unusual if we can judge by the fact that only 4 cases, controlled by phrenicotomy, have been reported in recent literature.^{1,2,3,4} Smith⁵ in a paper published in 1926 on the respiratory disturbances of encephalitis described a case seen in 1923 which must have been similar to the ones the author is reporting. Phrenic section had not been suggested at that time and his patient was not relieved.

Welchsler⁶ defines a tic as "A sudden, abrupt, rapid, involuntary contraction of a muscle or a group of functionally related muscles. It is generally clonic, but if the movements follow in very rapid succession the contractions may become more or less tonic. Every tic has what seems to be a functional pattern or an ideational purpose, although it may appear in exaggerated or even grotesque form. . . . Like most abnormal movements, tics are aggravated by emotion and cease during sleep." He also says "I would merely urge that one pause considerably before attaching a label of hysteria to an involuntary movement just because it follows a pattern."

Case Reports. CASE 1.—Miss B. W., white, single, aged 20 years, was seen first in consultation with Dr. M. C. Smith of Simpsonville, S. C., on February 1, 1928. Her mother, father, several brothers and sisters are well

and hardy people engaged in farming. There is no neurologic taint on either side. She had influenza twice, 1918 and 1919, and there were no complications. She has had no illness since that could be considered influenza or even suggestive of epidemic encephalitis. The history of the present illness is given in some detail because of the possible relationship between repeated intestinal obstructions and diaphragmatic tic. In October, 1926, she was operated on for acute weeks later rapidly formed adhesions caused an acute intestinal obstruction requiring the second operation. Until March 10, 1927, she was well, developing on this date her first respiratory distress, characterized by a very rapid, jerking sort of hiccup at a rate of 100 a minute. This lasted without let up except when asleep until April 13 when it subsided spontaneously. There was no similar distress until mid-August when she had a second attack lasting about 12 hours. She was then well until November, 1927, when she became obstructed for the second time, requiring a third abdominal operation. Convalescence was stormy, but after 3 weeks she returned home and progressed nicely. On January 23, 1928, the third attack of diaphragmatic spasm occurred. This had lasted a week when I saw her at home. The patient was in bed, obviously distressed and rather exhausted by a most harassing respiratory tic. There was no visible thoracic breathing, though she was apparently breathing rapidly and jerkily with a sort of grunt that could be heard throughout the house. This was at a rate of 90 a minute and with each grunt the lower borders of the ribs jerked rhythmically. The lungs were negative on examination and normal thoracic breathing could be done voluntarily, but during a full inspiration the rapid jerk continued and could be felt in the epigastrium. The heart was regular at 86, and was normal. Blood pressure was 105 systolic and 70 diastolic; the temperature 98°. The next day she was brought to a hospital for observation. There several specimens of urine varied from neutral to alkaline to litmus and were otherwise negative. Routine blood counts, smears and a blood Wassermann were negative. Fluoroscopic examination showed the right diaphragm to be more actively involved in the spasm than the left. The right was almost tonically contracted and showed a very rapid flutter synchronous with the grunt. The left side showed some jerkiness but was evidently not involved as was the right. In view of the fact that two other similar attacks had subsided spontaneously she was kept under observation for a second week. The tic persisted at a rate from 90 to 110 a minute. It would subside when she could be put to sleep, which proved very difficult, requiring large doses of morphin with scopolamin to quiet her for 3 or 4 hours. During sleep so induced there was no apparent disturbance of the respiratory mechanism, but the instant she would awake the tic returned.

After 2 weeks of persistent distress it was decided to section the phrenics to control the spasm as recommended by Gamble *et al.* and by Dowman. On February 6, Dr. Dowman saw the patient and promptly concurred in this plan. He then exposed the right phrenic under novocain anesthesia and proved it by faradic stimulation, which produced a severe pain in the right scapular region, repeating the observation previously reported by him. The nerve was then frozen white for about an inch with a spray of ethyl chlorid. The tic stopped so abruptly as to be dramatic and the respirations immediately became normally thoracic at a rate of 22 a minute. It having thus been proved that the attack involved only the right diaphragm, the nerve was then divided and the free ends dropped into the wound. Fluoroscopic examination after this operation showed the right diaphragm elevated and almost immobile. Three days later she was allowed to return home breathing perfectly comfortably.

On March 1, just 3 weeks after the phrenicotomy, she was brought back to the hospital with the third intestinal obstruction, which was again relieved by freeing the bands of dense adhesions. On March 13, while

convalescent from the last abdominal operation, there suddenly appeared a spasm of the left diaphragm with a tic averaging 140 a minute, identical in every respect with the others except that fluoroscopic examination showed this one to involve the left side and that the right diaphragm was still paralyzed. After waiting 4 days for this attack to subside, we decided to freeze the left phrenic, which was done on March 17, by Dr. T. B. Reeves of Greenville. Promptly on freezing the left nerve the tic ceased and the patient became comfortable, but unfortunately this lasted only 48 hours when the tic reappeared at a rate of 100 to 110. March 20, the left phrenic was again exposed through the same wound and this time about 5 cm. removed. After cutting the nerve at the same point where freezing it 2 days before had controlled the tic, we were surprised when the spasm only partly subsided. After searching a few minutes a small branch higher up was found and when this was cut the tic disappeared instantly. For an hour or 2 the patient complained of some vague distress on breathing, but the respirations were regular, normally thoracic and appeared comfortable.

In September, 1928, the patient was observed and at this time she seemed well and had gained 20 pounds. There was no respiratory distress and none had occurred since the operation on March 20. Constipation was a problem and she was taking 2 ounces of castor oil daily. On fluoroscopic examination the right diaphragm was found functioning normally and the left still out. It is of interest to note that the right phrenic had regenerated within a period of 7 months after section.

The patient was next seen in December, 1929, when the fourth obstruction by adhesions occurred. There had been no attacks of diaphragm spasm now for 20 months. At operation the entire right lower abdomen was filled with adhesions involving the lower end of the ileum, the cecum and the ascending colon. The obstructing bands were released and the patient relieved. On December 19, 10 days after this operation, the diaphragmatic tic again appeared, identical with the other attacks and averaging about 90 a minute. We found this time that the right side was involved and the left still paralyzed. On December 23, the right nerve was exposed, requiring some little search because of scar tissue and the fact that it was smaller than originally. The nerve was then avulsed with prompt control of the tic. She was discharged December 30, but on January 3, 1930, she was brought back with the fifth obstruction. At this time it was decided to do a more radical operation and the last free portion of the ileum was anastomosed to the descending colon. Convalescence was uneventful and the patient discharged in better health than I had ever seen her. Unfortunately the patient did not continue to improve but developed an intractable diarrhea a few months later and died. She suffered no respiratory distress during the time that she lived after both phrenics were resected, though she was never very active because of the diarrhea.

CASE 2.—Mrs. R. F., white, married, aged 21 years, was seen at her home in consultation with Dr. L. L. Richardson of Simpsonville, S. C., on January 1, 1929. This patient lived on a neighboring farm near the first case, though both families assured me that she had never seen the other girl during an attack. The story here is different and is quite in line with the 4 cases previously reported. Three weeks before I saw this patient she had a mild attack of influenza from which she had apparently recovered until 3 or 4 days before, when she became very restless, complained of headache and of double vision, and a moderate fever reappeared. During the morning of January 1, she suddenly developed a diaphragmatic tic identical with that described in the first case. The mother of my first case made the diagnosis here before I saw the patient. Here the rate average 120 a minute and presented the same rapid, jerking, grunting spasm as described above. In this patient we have a definite attack of epidemic encephalitis with the onset of the tic on the third or fourth day of the disease. She was observed

for 4 days, during which time the symptoms of encephalitis became more pronounced and the tic continued. It was difficult to get this patient to sleep, but as in the first case, during sleep the respirations were normal. Except for the neurologic evidences of the encephalitis all examinations were negative. Two urine specimens were reported slightly acid to litmus. The following day she was brought to the hospital where fluoroscopic examination showed the right diaphragm to be more actively involved in the tic.

On January 5 the right phrenic nerve was exposed and its control of the tic proven by freezing with ethyl chlorid, after which it was cut in two and both ends dropped into the wound. The patient had no further respiratory distress and within a week she was better so that she was discharged.

Three months later the tic reappeared, though now it occurred only every 3 or 4 weeks and lasted a few hours. She was seen at the office soon after this and the fluoroscopic examination showed that the right diaphragm was again functioning normally. Here the right phrenic had regenerated within 3 months after section. At this observation definite psychic changes were noted and these were regarded as the result of the epidemic encephalitis 4 months before. These infrequent attacks occurred only a few times and on each occasion seemed to be precipitated by some emotional flurry. For the past 6 months she has had no attacks and has seemed to be in much better health.

Summary. Two cases of diaphragmatic tic relieved by section of the phrenic nerves are placed on record.

These cases confirm several observations made by the other authors: (1). In Case 1, Dowman repeated his observation that faradic stimulation of the proximal end of the sectioned phrenic produces pain in the scapular region. (2) Case 1, showed a neutral to alkaline urine, probably due to overventilation with elimination of alkali in the urine as suggested by Gamble *et al.* (3) Case 1, required resection of both phrenics for final control, confirming Skillern's observation that freezing or section was only of temporary value.

The phrenic nerve regenerated in both cases after section, within 7 months in the first case and 3 months in the second.

Both patients were young women living on neighboring farms. One patient developed the tic during a definite attack of epidemic encephalitis, while in the other and more distressing case no history of an illness that might be consider epidemic encephalitis could be obtained. The inevitable diagnosis of hysteria had been made in the first case by several consultants before the condition was recognized.

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THE RELATION OF THE SYMPATHETIC NERVOUS SYSTEM AND GENERALIZED LYMPHOID HYPERPLASIA TO THE PATHOGENESIS OF EXOPHTHALMIC GOITER AND CHRONIC LYMPHATIC LEUKEMIA.

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Similarity of Exophthalmic Goiter and Chronic Lymphatic Leukemia.

Exophthalmic goiter and chronic lymphatic leukemia are particularly characterized by an elevated basal metabolic rate. In no other condition, except chronic myeloid leukemia, is the incidence of this disturbance so high.

This similarity may be especially significant because Lugol's solution induces a strikingly similar clinical remission with reduction of the basal metabolic and pulse rates in certain patients with chronic lymphatic leukemia and Graves' syndrome.^{1,2} This parallelism is still more obvious in a study of the pathologic physiology and salient clinical signs and symptoms which have been universally associated with these maladies.

Clinical Features. The classic symptoms of exophthalmic goiter are remarkably similar to those of chronic lymphatic leukemia,^{3,2} although they are usually much less intense in leukemia even in the presence of an equally elevated basal metabolic rate. Acute exacerbations and remissions in exophthalmic goiter have been widely recognized, while Minot and Isaacs⁴ have more recently emphasized a similar phenomenon in the chronic leukemias.

The eye signs, which have been considered classic of exophthalmic goiter, are most probably manifestations of a hyperactive sympathetic nervous system.^{5,6,7,8,9} Their widespread prevalence in conditions other than Graves' syndrome has been recently reported by Friedgood.¹⁰ The relative frequency of these eye signs in chronic lymphatic leukemia is probably of similar significance.

Ocular phenomena were detected in 6 of 10 patients with chronic lymphatic leukemia; while several had as many as three different eye signs.

TABLE 1.—OCULAR PHENOMENA IN CHRONIC LYMPHATIC LEUKEMIA.

Sign.	No. patients positive.
Unilateral prominence of right eye	5
Bilateral exophthalmos	4
von Graefe's sign	2
Kocher's sign	2
Dalrymple's sign	2

Palpable splenomegaly and generalized lymphadenopathy are accepted and widely recognized physical findings in chronic lym-

phatic leukemia. However, their prevalence in exophthalmic goiter is not generally recognized.

The spleen is definitely enlarged at autopsy in exophthalmic goiter,^{11,12,13,14,15,16} even to the point where one may detect it clinically by palpation and percussion in about 20 to 30 per cent of the cases.^{17,18,16} Sainton and Emond¹⁸ were unable to detect a splenomegaly in 22 control patients with simple endemic goiter.

Numerous investigators have also pointed out the prevalence of generalized lymphoid hyperplasia which can be detected clinically in the regional lymph nodes of the neck,^{11,12,19,20,21} and in the pharyngeal, faucial and lingual tonsils.¹³

It is probably significant, in the presence of this widespread splenolymphatic hyperplasia, that certain authors have reported a relative as well as an absolute lymphocytosis in 30 to 67 per cent of patients with Graves' syndrome.^{22,23,24,25}

Plummer²⁵ could not detect any relationship between the degree of mononucleosis, the height of the white blood cell count and the severity of symptoms; but Menkin²⁴ has recognized that mononucleosis is more likely to occur in association with exophthalmos and evidence of a hyperactive sympathetic nervous system.

Pathologic Features. The pathologic anatomy of exophthalmic goiter is no less striking than its clinical signs and symptoms. As far as is now known there is only one pathologic finding which has been universally reported in Graves' syndrome; but others of occasional or frequent occurrence are probably also significant.

Although small foci of lymphoid tissue can be occasionally demonstrated in normal thyroid glands,^{26,27,28,12} extraordinary lymphoid hyperplasia with the development of well formed germinal centers^{29,30,31,11,12,32,26,34,35,36,37,38,39,40,20,21,15,41,42,43} is an almost constant pathologic change in the thyroid gland of exophthalmic goiter.

Apparently there is no essential difference in the basal metabolic rate between those cases showing extensive epithelial and lymphoid hyperplasia and those having only lymphoid hyperplasia.⁴³ In many of the latter, the basal metabolic rate was recorded as high as +100 per cent.

It is even more significant that these changes in the thyroid are only a part of the generalized increase in lymphoid tissues throughout the body, involving the regional lymph nodes, especially of the neck and the pharyngeal, faucial and lingual tonsils. Scattered foci of lymphoid cells also occur in nests throughout the viscera and especially in the kidneys, muscles, liver and even in the bone marrow; while Peyer's patches and the solitary follicles of the intestines are also universally hyperplastic.^{30,23,31,11,12,34,13,14,17,33,18,19,44,20,21}

The splenomegaly which is often found at autopsy in exophthalmic goiter (*vide supra*) is also marked by a generalized lymphoid hyperplasia with enlargement of the Malpighian corpuscles. The latter are characterized by that type of lymphoid exhaustion which War-

thin recognizes as a fundamental constitutional disturbance in exophthalmic goiter (thymicolymphatic constitution).

It is, of course, well known that the thymus is also abnormally enlarged and persistent in the great majority of patients with exophthalmic goiter.^{11,12,45,46,13,39,20,47}

In general, the changes in the thymus are supposed to parallel those in the other lymphoid tissues of the body, and MacCallum states that "descriptions of the histologic changes are most contradictory, but it seems that they may represent an accentuation of the condition corresponding to the age at which the disease developed."

Significance of Lymphoid Hyperplasia in Graves' Syndrome. Although pathologists have been cognizant of this widespread lymphoid hyperplasia in exophthalmic goiter, its general importance has not received sufficient attention, because of the veil of mystery which seemed to shroud its specific significance in the pathogenesis of the malady. However, the fact that Lugol's solution has a strikingly parallel effect in two diseases, both characterized by a specific and similar disturbance in the lymphatic system and rate of oxygen consumption, suggests that there may be a fundamental disorder common to both, and responsible for the remarkable similarity in their clinical signs and symptoms.

The Sympathetic Nervous System. The relation of the sympathetic nervous system to the pathogenesis of exophthalmic goiter has been the object of investigation and interest for many years. Numerous observations have been attempted to determine the effect of experimental stimulation and resection of these ganglia and nerve trunks; but a satisfactory interpretation of these results has not been forthcoming, and the question is still *sub judice*.

The cervical sympathetic ganglia of exophthalmic goiter have received particular attention by Greenfield,⁴⁸ Wilson,⁴⁹ and Wilson and Durante.⁵⁰ Greenfield found a subacute inflammatory lesion, characterized by swelling and hyperemia, in addition to leukocytic infiltration and subsequent degenerative changes of the cervical sympathetic ganglia. The central nervous system (especially the medulla oblongata) was also found to be involved in a similar process. Wilson and his colleagues, however, were impressed with the degenerative changes in these ganglia, and called attention to fatty deposits within the ganglion cells, atrophy and reduction in their number and a diffuse fibrosis of the entire ganglion.

These changes in the cervical sympathetic ganglia of patients with exophthalmic goiter are certainly of immediate interest in a syndrome which is characterized by such marked evidence of autonomic imbalance.^{51,52,10} The problem seems well worthy of further investigation from this point of view.

The Pathology of Chronic Lymphatic Leukemia. The important pathologic findings of chronic lymphatic leukemia have been stud-

ied extensively, and are well recognized. Even a superficial comparison of the latter with the pathology of exophthalmic goiter reveals the striking similarity which seems to exist between the two.

The immediate and obvious difference is almost purely a quantitative one—the lymphoid and splenic lesions being much less extensive in exophthalmic goiter than in chronic lymphatic leukemia.

In lymphatic leukemia, there is usually a generalized lymphadenopathy with enlargement of the solitary nodules and agminated lymphatic tissue in Peyer's patches. The liver, kidneys, lungs and bone marrow may also be well infiltrated with lymphocytes. The spleen is usually easily palpable, and the Malpighian bodies, as in Graves' syndrome, are enlarged. In lymphatic leukemia, however, the hyperplastic lymphoid tissue disturbs the normal architecture of the stroma, so that the pulp is somewhat distorted but still discernible.

Chronic lymphatic leukemia has been reported without the presence of enlargement of the spleen or regional lymph nodes.^{53,54} The French speak of this as "*forme medullaire de la leucemie lymphatique chronique*." Bensis and Gouttas⁵⁴ quote cases from Walz, Pappenheim, Konmoezy, Dennig, Naegeli and Aubertin Charles, and report two new instances.

Various investigators disagree concerning the changes in the thymus in chronic lymphatic leukemia. Thorpe,⁵⁵ DeSautelle and Wood,⁵⁶ and Poensgen⁵⁷ have reported isolated cases of thymic hypertrophy associated with chronic lymphatic leukemia; while Ordway and Gorham⁵⁸ state that "the thymus gland is usually large, and may even show tumor-like nodules and infiltration of the surrounding tissue. Histologically, the change is comparable to that found in the lymph glands." However, Ewing,⁵⁹ Margolis,⁶⁰ and Schridde⁶¹ state that in their experience true thymic hyperplasia is either rare or absent in chronic lymphatic leukemia. The researches of Williamson and Pearse,⁶² and Blackford and Freligh⁴⁵ suggest that the changes in the thymus gland are more closely related to those in the thyroid gland in particular, rather than to the hyperplasia of the lymphoid structures in general.

Noteworthy Variations. The presence of lymphocytosis is expected in chronic lymphatic leukemia, but the remarkable occurrence of aleukemic phases is of interest, because they are found in a disease which may be characterized by the absence of other salient clinical and pathologic phenomena, such as lymphoid hyperplasia, splenomegaly, elevated basal metabolic rate and tachycardia. The significance of these departures from the usual type of syndrome is unknown at the present time.

A similar state of affairs exists with regard to exophthalmic goiter, because such characteristic phenomena as increased basal oxygen consumption, lymphocytosis, tachycardia and exophthalmos may

be absent in the presence of an otherwise typical clinical syndrome. The discovery of the mechanism and significance of these interesting variations will undoubtedly lead to a better understanding of the pathogenesis of Graves' syndrome and chronic lymphatic leukemia.

The Physiology of the Sympathetic Nervous System. The predominance of the signs and symptoms of sympathetic nervous system hyperactivity in these maladies suggests that this system plays a rôle of paramount importance in their pathogenesis. It is not known whether this fundamental disturbance involves the *central* or *peripheral* connections of the sympathetic nervous system, but the subjective and objective manifestations of its hyperactive state are well recognized. The subjective phenomena include various types of nervousness, palpitation and emotional instability. The objective signs are expressed in terms of its influence on tonicity of musculature (tremor), cardiac rate (tachycardia), secretions of sudoriferous glands (sweating), the ocular manifestations (exophthalmos, lid-lag, lid-spasm, Dalrymple's and Kocher's eye signs) and vasomotor instability.

The Sedative Action of Iodin. Iodin appears to have a striking ability to induce a remission in the signs and symptoms of this sympathetic hyperactivity. The depression of the general emotional instability and the relief from the tachycardia, sweating and vasomotor phenomena suggest that iodine has a "selective sedative action" on the sympathetic nervous system.

The concomitant decrease of the basal metabolic rate, following iodine therapy in certain instances of exophthalmic goiter and chronic lymphatic leukemia, may signify that at least a portion of the mechanism responsible for its elevation is exerted through the sympathetic nervous system, and that its depression is also accomplished by the "selective sedative activity" of the iodine. It is, of course, quite possible that this metabolic disturbance is secondary to various influences, only one of which responds to what one may term the "sedative action" of iodine. To a certain extent, this may explain the *modus operandi* of those cases in both maladies which do not respond to Lugol's solution in the expected manner.

This conception assumes even greater significance if one considers that increased nervous tension, secondary to any cause whatsoever, is frequently responsible for a definite elevation in the basal metabolic rate; and that the effect of epinephrin, an activator of the sympathetic nervous system (palpitation, tremor, tachycardia, vasomotor and emotional instability) is characterized by a transient but nevertheless significant elevation of the basal metabolic rate.^{63,64,}

65,66,67,68,69,70,71,72

Discussion. *The Relation of the Thyroid Gland to Exophthalmic Goiter.* If the Merseburg triad of exophthalmic goiter is present in association with an increased basal metabolic rate and the peculiar

nervous manifestations of the disease, the pathologic changes in the thyroid gland may be those of a diffuse parenchymatous hyperplasia with marked diminution of the colloid substance.

The more striking syndrome, however, includes those instances in which marked symptoms of exophthalmic goiter occur in association with either a normal thyroid gland or an altered thyroid without evidence of hyperplasia.^{73,74,75,23,11,12,76,77,13,34,36,78,46,38,39,40,79,80,81,20,21,43}

Speaking of those instances in which the thyroid is normal in association with an abnormally persistent and hypertrophic thymus, Klose and Hellwig⁴⁶ go so far as to write "wir sehen in diesem Fall einen erneuten Beweis für das Vorkommen eines rein thymogen Basedow, ohne spezifische Schilddrüsen Veränderung."

Furthermore, it has been generally disregarded that many other diverse lesions (syphilis, miliary tuberculosis, extensive hemorrhage, ligneous thyroiditis, inflammatory changes, neoplasm) have been discovered in the thyroid gland in association with exophthalmic goiter and that the syndrome has been reported accompanying such acute infections as typhus fever and acute articular rheumatic fever.^{13,82,20}

Kocher²³ said "it has been difficult for those who have examined large series of cases and also for those who see a great deal of other diseases of the thyroid gland, to accept the above mentioned changes (proliferation of epithelium, which assumes the cylindrical type, the liquefaction of colloid, etc.) as being specific for exophthalmic goiter. We find the same enlargement of follicles with formation of papillæ and high cylindrical cells, together with the decrease in thick colloid, in glands of normal size, in hypertrophic as well as nodular goiters, without the slightest symptoms of exophthalmic goiter."

Hyperplasia of the Thyroid Gland in Myxedema, Endemic Goiter and Postoperative Subtotal Thyroidectomy. Further evidence against the specificity of thyroid hyperplasia for exophthalmic goiter may be inferred from the fact that it is not essentially different from that found in certain instances of animal and human *myxedema*,^{83,84,91,92} *endemic goiter*⁸⁵ and following *partial thyroidectomy*.^{86,87,11,12}

Relation of Iodin to the Thyroid Gland. The significance of these observations becomes even more apparent if attention is directed to the relation of iodine to the histologic architecture of the thyroid gland, and its ability either to prevent the occurrence of postoperative compensatory hyperplasia and the hyperplasia of endemic goiter, or induce their involution to the colloid state.^{88,89} These investigators have finally concluded that all thyroid hyperplasias are anatomically, chemically, and biologically identical, and secondary to a relative or absolute iodine deficiency. -

Extensive investigations by Kocher,²³ Cattell,³⁸ Rienhoff,⁴⁴ Giordano,⁴⁰ Sager,⁴¹ and Holst and Lunde⁹⁰ have demonstrated

that the therapeutic use of iodine causes a process of involution to the colloid state in hyperplastic thyroids from patients with Graves' syndrome, similar to that reported by Marine and his co-workers for endemic goiter.

Hyperplasia-Hyperthyroidism Theory and an Alternate Conception. These data render it obvious, therefore, that the theory of a hyperthyroidism secondary to and dependent upon hyperplasia of the thyroid gland is not entirely adequate to explain the nature and pathogenesis of Graves' syndrome.

There is a natural tendency in medicine to classify a group of clinical syndromes according to their salient clinical characteristics, if their etiology is obscure.

Chronic lymphatic leukemia and exophthalmic goiter likewise appear superficially to be wholly unrelated clinical syndromes. However, a more careful investigation indicates that a striking and fundamental parallelism exists between these two syndromes. Both maladies are characterized by an elevated basal metabolic rate and by the obvious signs and symptoms of an hyperactive sympathetic nervous system (relative tachycardia, tremor, abnormal sweating, emotional and vasomotor instability, exophthalmos and associated eye signs). Generalized lymphoid hyperplasia and splenomegaly occur in both diseases; and lymphocytosis is recognized as a typical change in the peripheral blood circulation. All of these phenomena differ only in a *quantitative* manner.

The evidence of sympathetic nervous system hyperactivity is much less intense in chronic lymphatic leukemia, even in the presence of an equally elevated basal metabolic rate; but the lymphoid reaction is less conspicuous in Graves' syndrome.

The available data suggest that the signs and symptoms of both chronic lymphatic leukemia and exophthalmic goiter are expressed, in varying degrees, through the hyperactive state of the sympathetic nervous system.

The influence of iodine upon the pathologic physiology of the sympathetic nervous system is usually of a sedative character, but may act as a stimulant under conditions which are unknown at present.

The intimate and frequent association of generalized lymphoid hyperplasia, clinical manifestations of sympathetic nervous system hyperactivity and elevated oxygen consumption may be of more than casual significance.

Summary and Conclusions. Lugol's solution has a strikingly parallel effect upon the clinical phenomena of exophthalmic goiter and chronic lymphatic leukemia; and, conversely, does not ameliorate the signs and symptoms of true hyperthyroidism induced by the ingestion of active thyroid substance.² These facts, in addition to the similarity which exists between the clinical picture and pathology of chronic lymphatic leukemia and exophthalmic goiter, indicate

that these maladies are primarily independent of thyroid dysfunction. Exophthalmic goiter is probably not due to a hyperthyroidism, and its elevated basal metabolic rate and tachycardia seem to be independent of a hypothetical hypersecretion from a hyperplastic thyroid gland.

The sympathetic nervous system and the lymphatic system play a significant rôle in the pathogenesis of exophthalmic goiter and chronic lymphatic leukemia; and the effect of iodine is probably intimately related to the pathologic physiology of the sympathetic nervous system.

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THE INEFFICACY OF SPLEEN EXTRACT IN THE TREATMENT OF LYMPHATIC LEUKEMIA.

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For clinical direction and scientific accuracy it is highly important that negative as well as positive results be recorded. Last year Pearce¹ reported an isolated case of acute lymphoblastic leukemia in which intramuscular injections of a 40 per cent albumin-free solution of hog spleen alternating daily with a 20 per cent solution of liver extract, supplemented by the oral administration of liver extract, effected an apparently complete recovery. In all 5 injections of the liver extract and 10 of the spleen extract were made, but the oral administration of the liver extract was continued for over 3 months. Since liver and its extracts have proved without influence upon the course of leukemia,^{2,3} it was natural to assume that the spleen extract was the important element in the therapeutic result. Shortly following the report of Pearce came a second clinical experience suggesting the efficacy of spleen extract intramuscularly administered in leukemic states. Busman and Woodburne⁴ recited the clinical improvement in the cutaneous lesions and the disappearance of a leukemic blood picture in a patient receiving a series of 24 intramuscular injections of spleen extract at semiweekly, weekly and biweekly intervals. An assessment of the benefit of this therapy is difficult for the reason that a series of 4 Roentgen-ray treatments had preceded the trial of spleen extract and the most marked improvement in the leukocytic formula had attended Roentgen-ray therapy.

Pearce¹ gave spleen extract "on the grounds of the connection in the etiology and pathology of the disease and the imperfectly understood functions of the spleen." Busman and Woodburne⁴ state that "the possible allergic tuberculomatous type of skin lesion associated with the blood picture of a hematopoietic disease led us to use spleen extract as a therapeutic agent."

For the time more interested in the end than means to that end, the promise of a therapeutic agent of benefit in lymphatic leukemia led us to immediate studies in the preparation of spleen extracts.

Neither of the above reports had included this detail. Several different methods were pursued and the products labeled as follows:

Methods. *Spleen Extract A:* 400 gm. of hog's fresh spleen was minced and mixed with enough water to make 1000 cc. This mixture was then boiled and filtered first through cheese cloth and then several times through filter paper until the filtrate became brilliantly clear. This final filtrate was then candled through a sterile medium Mandler filter, cultured for sterility and bottled aseptically:

Spleen Extract B: 400 gm. of hog's fresh spleen was minced and mixed with 600 cc. of 95-per cent alcohol. This mixture was rendered more intimate by shaking for 15 minutes, after which it was kept in a cold room. Thereafter it was removed to a warm room for 24 to 48 hours. Then it was squeezed through cheese cloth and filtered through paper. The filtrate was evaporated to about 300 cc. *in vacuo* at 40° C. By this manipulation most of the alcohol was removed and much of the lecithin precipitated. It was next filtered again, but the finely dispersed lecithin passed through the filter. To the milky filtrate was added about 1 per cent fuller's earth. The whole was thoroughly mixed and filtered through filter paper; whereupon the filtrate became clear and of a golden brown color. This clear filtrate was then candled through a sterile medium Mandler filter, tested for sterility and bottled aseptically.

Spleen Extract D: While still warm at slaughter the spleens were removed from swine and plunged into boiling water. After boiling for 5 minutes they were hashed to a fine pulp and about one-third of their volume of distilled water added. This mixture of 3 parts of spleen pulp plus 1 part of water was gradually brought to a boiling point. Its reaction was adjusted immediately to pH 5.4 by the addition of $\frac{N}{4}$ hydrochloric acid. The mash was boiled for 5 minutes and then squeezed through cheese cloth. The liquid was filtered through filter paper and the filtrate concentrated to one-quarter its volume by distillation at 85° C. *in vacuo*. This concentrate, which was quite turbid, was candled without preliminary clarification through a medium Mandler filter. The gold yellow filtrate was tested for sterility and bottled aseptically. Six hundred cc. of spleen extract D were derived from about 6 kilos of fresh spleens.

Spleen Extract C: This extract was prepared in the same manner as D, except that the spleens were ground at the packing-house and boiled immediately without adjustment of pH. This control of the reaction was made at the laboratory and the mixture boiled again.

Spleen Extract 6 B: A portion of spleen extract B was evaporated under reduced pressure to one-sixth of its volume, candled, tested for sterility and bottled.

Powdered Spleen Extract D: 400 cc. of spleen extract D was evaporated over a water bath to a syrupy consistency and poured into a large volume of 95 per cent alcohol. The sticky mass was collected and dried in scales and from this amount of liquid extract 30 gm. of dry extract was obtained. This dry extract represented about 4 kilos of fresh spleens. The dry extract was divided into 3 gm. lots, each representing 400 gm. of fresh spleen.

(In the clinical trial of these several extracts the substance will be referred to by letter.)

Case Reports. CASE 1.—The first patient appearing for treatment was a 10-month female infant presenting the classical features of lymphoblastic leukemia. The history dated back about a month when the infant became tired in appearance and "not as good natured" as usual. Ten days prior to admission lumps were noted behind both ears and the hair began to fall out. The normal weight gain had ceased with the onset of the present illness but there had been no weight loss. The appetite had been reduced. There was some bleeding from the nose and mouth.

The infant was fretful. A bluish-gray discoloration and puffiness was apparent about the eyes. A general lymphadenopathy was remarked in the accessible lymph nodes. The liver extended 4 cm. below the costal margin and the spleen, 7 cm.

The blood examination constituted the most important laboratory detail: Hemoglobin, 28 per cent; erythrocytes, 2,830,000; leukocytes, 362,500; Differential: neutrophils, 0.8 per cent; lymphocytic series, 99.2 per cent; platelets, 10,000.

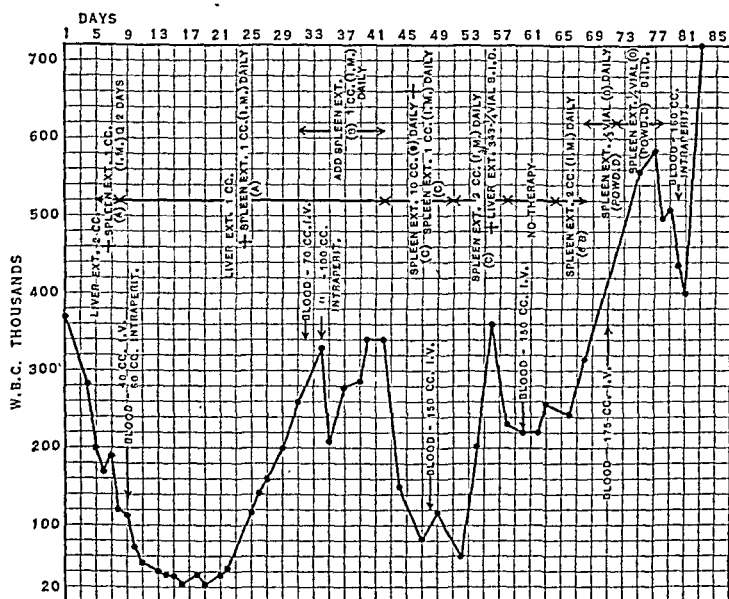


FIG. 1

The accompanying chart of the blood picture (Fig. 1) gives an accurate analysis of the therapy. In all this patient received 57 intramuscular injections of various spleen extracts in doses of 1 to 2 cc. over a period of 63 days. To this were added several courses of spleen extract by mouth, 5 blood transfusions and liver extract, orally and intramuscularly. Several incomplete remissions occurred but these were apparently without relation to treatment. The objective improvement in the general condition of the infant was notable during these periods of remission in the blood picture. Interestingly, each successive remission was less adequate than its predecessor and each relapsing peak of leukocytes higher than the previous until a level of 725,000 was reached the day before death. While the clinical course of this case was unusual in its remarkable remissions (objective and blood) and in its duration of almost 4 months, yet occasional instances of this type are seen contrasting sharply with the usual progressive downward course of much shorter duration in lymphoblastic leukemia.

A second trial of the spleen extract was afforded by Case 2, a white male, aged 29 years, admitted to the Wisconsin General Hospital on February 1, 1931, with acute lymphoblastic leukemia. The history which was unusual merely in the primary cutaneous lesions, which leukemic infiltrations formed a predominant part of the picture to the end. The first of these nodules was noted about the left ear after Christmas, 1930; but shortly thereafter a vast number appeared over the entire body. The leukocytes numbered 49,900 on admission with 65 per cent lymphocytes of a very immature order. Because of the rapidly progressive superior cyanosis, venous engorgement of the neck and head and dyspnea from mediastinal pressure. Recent-

gen-ray therapy was utilized as a last resort. A series of 5 Roentgen-ray exposures effected considerable reduction in the size of the mediastinal lymph nodes with proportional improvement in the above mentioned pressure phenomena. Spleen extract B was injected daily intramuscularly in 2 cc. doses for 8 days during the first admission prior to the Roentgen-ray therapy without effecting any alteration in the blood picture, the local or the systemic situations. In fact, during the period of spleen extract exhibition the leukocytes rose from 40,900 with 61.5 per cent lymphocytic types to 62,000 with 94 per cent of this order.

After a period of about 2 weeks at home the patient returned to the hospital March 10, 1931. His condition had advanced markedly. The cutaneous nodules were more abundant and the mucous membranes of the nose and mouth showed similar lesions. The liver and spleen which on the previous admission had been somewhat enlarged, now extended 8 and 6 cm. below the costal margins, respectively. The hemorrhagic tendency was more marked as evidenced by petechiæ and epistaxis. The leukocytes at this time numbered 547,000 with 99 per cent lymphocytes (largely lymphoblasts). From March 15 until just before his death on May 13 this patient received daily intramuscular injections of spleen extract B or C in 5-cc. doses. The leukocytes ranged between 320,000 and 488,000 for 36 days after the institution of this therapy and then there occurred a progressive decline to an aleukemic state prior to death without apparent relation to treatment. Interestingly, the leukocytes the day before death were 6950 with 79 per cent neutrophils.

Only one further trial of spleen extract in the treatment of lymphoblastic leukemia has been available. In this instance the substance was administered to a patient *in extremis* and under the conditions no judgment of its efficacy could be formed. It has, however, been given to 3 patients with chronic lymphocytic leukemia and to one with eosinophilic leukemia. The results in all of these cases have been entirely negative. A brief outline of the treatment by spleen extract in each follows:

CASE 3.—A white female, aged 59 years, with chronic lymphocytic leukemia marked by cutaneous infiltration was readmitted on September 27, 1930. The local and general response to Roentgen-ray therapy (11 exposures) a month previously had been entirely satisfactory. The leukocytes fell from 46 to 20 thousand; but the lymphocytic percentage rose from 78 to 86.7. The basal metabolic rate over the same period of treatment dropped from +38 per cent to +18 per cent. Unfortunately an uncomplicated trial of spleen extract was not afforded on the second admission. However, during the first month of this period of hospitalization, when she received a series of 7 Roentgen-ray treatments, there occurred a rise of the total leukocytes from 25 to 35 thousand, the lymphocytic figures being 92 and 86 per cent respectively. Furthermore the response of the basal rate was less pronounced than on the earlier trial, a fall from +32 per cent to +26. On the other hand the cutaneous lesions were greatly improved. With the discontinuance of Roentgen-ray therapy spleen extract was begun. With several variations the intramuscular injections of spleen extract A or B, at times supplemented by intramuscular injections of liver extract, were continued until discharge, 34 days later. A total of 18 injections of 1 to 2 cc. of spleen extracts was given without appreciable effect upon the blood picture. The white cells numbered 37,000 at the conclusion of this period as compared with 35,000 at the outset and the lymphocytes were 92 per cent and 86 per cent, respectively.

CASE 4.—A white male, aged 56 years, presenting the classical features of chronic lymphocytic leukemia of 3½ years' duration was admitted to the

Wisconsin General Hospital on October 30, 1930. His prior treatment had consisted of repeated series of Roentgen-ray exposures over 2 years; but on this admission the severe secondary anemia and profound depression precluded further Roentgen-ray therapy. The leukocytes numbered 270,000 with 96 per cent lymphocytes. A series of 6 intramuscular injections of spleen extract B was administered on alternate days without appreciable effect upon the leukemic or the general condition.

CASE 5.—A female outpatient, aged 56 years, had suffered from chronic lymphocytic leukemia for 5 years. The condition of the skin, pain of perisplenitis and severe secondary anemia necessitated rest from Roentgen-ray therapy, which had held the major manifestations of the leukemia fairly well under control. Accordingly she was given a series of 8 intramuscular injections of 2 cc. spleen extract B on alternate days. The total leukocytic count at the outset of this therapy was 135,750 with 92 per cent lymphocytes; whereas at the conclusion the white cells numbered 220,750 with 97 per cent lymphocytes.

CASE 6.—A white male, aged 33 years, suffering from eosinophilic leukemia of 2½ years' duration, received a series of 10 intramuscular injections of spleen extracts B or C in 2-cc. doses over a period of 35 days, alternating with intramuscular injections of liver extract. On admission the leukocytes numbered 14,000 with 72 per cent eosinophils, while on discharge the leukocytic count was 12,500 with 62 per cent eosinophils. Such fluctuations had been frequently observed without relation to treatment.

Summary. It will be remarked that no such favorable effects as reported by Pearce,¹ and Busman and Wooburne⁴ have attended the use of various spleen extracts in the group of lymphatic leukemias above reported. In the cases of lymphoblastic leukemia (Cases 1 and 2) a fair and complete trial of the therapeutic influence of several spleen extracts was afforded. In Case 1 there was absolutely no maintained influence upon the course of the disease. In Case 2 the numerical leukocytic count fluctuated widely and toward the fatal termination there was a return of the normal leukocytic formula without coincident improvement in the general condition of the patient. The group of lymphocytic leukemias (Cases, 3, 4 and 5) treated with spleen extract did not offer fair trials of such materials because of the complicating Roentgen-ray therapy. Cases 4 and 5 in particular represented "burned out" types in which further therapeutic trial of any order would not constitute a real test of its efficacy. The case of eosinophilic leukemia (Case 6) showed no improvement from the use of spleen extract.

From these rather inadequate data it may be concluded that the spleen extracts prepared by the methods herein described were without therapeutic effect in the cases of lymphatic leukemia studied.

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REVIEWS.

NUCLEIC ACIDS. By P. A. LEVENE, The Rockefeller Institute for Medical Research, and LAWRENCE W. BASS, Mellon Institute of Industrial Research, now Assistant Director of Research, The Borden Company. Pp. 337; 14 figures. New York: The Chemical Catalog Company, Inc., 1931. Price, \$4.50.

THE publication of a modern review of nucleic acid chemistry constitutes a welcome addition to the literature. Since the publication of the monograph on nucleic acids by Jones decided advances have been made in this field, many of them having originated in the laboratory of the senior author. The present volume summarizes the progress made to date in this highly involved subject.

The important rôle played by titration curves and other physico-chemical measurements in determining the structure of nucleic acids is fully presented. Particular attention is also paid to the enumeration of the physical and chemical properties of the most important products of nucleic acid hydrolysis. Special emphasis is laid on the chemistry of purins and pyrimidins, whereas less space is devoted to the sugars since these have been dealt with in detail in various other monographs.

J. A.

MEDICINE, SCIENCE AND ART. By ALFRED E. COHN. Pp. 212. Chicago: The University of Chicago Press, 1931. Price, \$4.00.

WITH the welter of newly ascertained facts that is constantly being added to the medical sciences, it is highly desirable that more thought be given to the nature of the motives activating these accumulations, and especially is it profitable when these thoughts are expressed by one who has himself worked productively in these fields. We may not agree with all of the author's views. Of course, "all is not well with medicine," but it never has been. Particularly is this apt to be the case when rapid advances—the decades of today being more than equivalent to centuries of the past—make adaptations more difficult. Nevertheless, the volume of intelligent thought now being given to medical problems shows at least the healthy search for improvement that is taking place in this country.

The six essays reprinted from various sources ("The Difference Between Art and Science in Their Relation to Nature," "The Development of the Harveian Circulation," "Purposes in Medical Research," "Medicine and Science," "Physiology and Medicine," "The Hierarchy of Medicine"), bear directly on medical trends, except the first, which has obvious indirect relations. We agree, then, with the author as to the relatedness of his essays and agree,

too, with the main points of the policy that he has formulated for himself. Like him, we hold that the objects of art and science are but partly alike, that their methods are usually strikingly different; but that both have their roots in nature and in the experience of man, and that some attributes of the artist are often invaluable to the scientist—as well as the practitioner. We agree too that in the long run disease must henceforth be studied primarily by medical scientists and that it is as hard for the practitioner to contribute to his science as it is for the practising engineer to contribute to pure physics. The neutral ground between investigation and practice on the one hand, and the sister sciences on the other, these are crucial points that are chiefly analyzed in some detail in the essays at hand. If more of our profession could possess the general culture that the author betrays, the handling of both of these problems would be greatly simplified. E. K.

PROCTOSCOPIC EXAMINATION AND THE TREATMENT OF HEMORRHOIDS AND ANAL PRURITUS. By LOUIS A. BUIE, B.A., M.D., F.A.C.S., Section on Proctology, The Mayo Clinic, and Associate Professor of Surgery, The Mayo Foundation. Pp. 178; 72 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, \$3.50.

THIS manual of 170 pages and about 70 illustrations, most of which are original and valuable adjuncts to a clear understanding of the subjects therein, contains the latest information of the methods of treatment explained in a clear and concise manner: It is interesting to note that 1 out of every 5 cases seen in the Mayo Clinics between 1910 and 1922 with carcinoma of the rectum or sigmoid, had been operated upon for hemorrhoids or treated symptomatically for irregularity, thus indicating the urgent necessity of works on this kind being in the hands of the general profession.

The author wisely is opposed to the indiscriminate use of opiates, especially their use for the relief of pain in the postoperative period, for usually this drug adds fuel to the fire as it produces subsequent constipation, lessens the patient's ability to bear pain and in many instances has been known to produce addicts.

The nonsurgical treatment of hemorrhoids is thoroughly discussed, especially that of the injection method. Its limitations and dangers are fully covered. It is a question in the Reviewer's mind if he understood the author's statement correctly, that in said cases the region is divided into 4 sections or quadrants and each of these may be treated over a period of 4 succeeding days. The Reviewer would question such a procedure, as the reaction would more than likely produce serious trouble, especially would this be the case if the advice were to be followed generally by those not so experienced as Dr. Buie.

The treatment of that most distressing condition known as anal pruritus is considered in a most thorough manner, and after discussing various means and measures employed by others the author indicates his choice of treatment.

L. A.

MEDICAL ADMINISTRATION OF TEACHING HOSPITALS. By EMMET B. BAY, M.D. Pp. 136. Chicago: University of Chicago Press, 1931. Price. \$2.00.

A VALUABLE and interesting discussion of the important problems of medical administration and how they are being handled in 19 teaching hospitals, together with the conclusions of the author as to their best solution. Some of the topics considered are: The admission of patients, contact with the referring physician, the allocation of beds to services and specialties, medical records, organization of the attending staff, general administrative organization, administration duties of clinicians and residents. While these matters are considered from the standpoint of the teaching hospital, they nevertheless have practically the same aspects in most hospitals. The Reviewer finds himself heartily in accord with the author's views, and feels that if members of hospital managing boards as well as administrators and the staff personnel would familiarize themselves with this little book they would be helped greatly in solving the problems which they have in common.

R. K.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY. Vol. VII, July, 1931. Pp. 441; 35 plates. Baltimore: The Williams & Wilkins Company, 1931. Price; \$10.00.

VOLUME VII of the *Annals of the Pickett-Thomson Research Laboratory* is divided into 3 sections, dealing with the rôle of the streptococci in erysipelas, skin diseases and measles.

Quotations are freely made from the 1600 references on the organisms found in these 3 conditions, their specificity, cultural and biologic characteristic production and efficacy of antisera, antitoxins, etc. Each section is supplemented with photographs of recognized type organisms in smear and on culture; for erysipelas, Birkhaug; for measles, Tunncliffe, Ferry and Fisher, etc. The authors also illustrate a small Gram-negative bacillus that they isolated from the throats and skin of cases of measles.

However, they conclude in their summary "further careful investigation is required with regard to the bacterial flora found in the respiratory tract and in the blood, etc., of measles cases. The organism of Caronia, a specific streptococcus, and the pleomorphic Gram-negative bacilli described by the authors, all require further investigation before they can be entirely ruled out of account."

"The cause of measles has not yet been discovered, and it seems likely that the disease is caused by an invisible noncultivable filter-passing virus."

They are "still convinced of the great value of Crowe's medium in the differentiation of the multifarious species of streptococci" and offer promise of progress by attempting to standardize its preparation, controlling moisture content, etc.

This volume forms a worthy successor to previous issues and is a mine of information on the bacteriology, biology and treatment of erysipelas, measles and various skin diseases. J. C.

EXPERIMENTAL STUDIES IN THE COURSE OF PARATYPHOID INFECTIONS IN A-VITAMINOTIC RATS. By H. C. A. LASSEN. Translated from the Danish by HANS ANDERSEN, M.D. Pp. 248; illustrated. Copenhagen: Levin and Munksgaard, 1931.

A CAREFUL review of the clinical and experimental literature upon the resistance to infections in the A-vitaminoses is given.

The author then reports in detail his own experiments upon the resistance of rats upon optimal and A-vitaminotic diets, to infection by ingestion of organisms belonging to the paratyphoid group. He concludes that the lowered resistance of the avitaminotic group is directly related to the vitamin deficiency.

The translation is satisfactory, although in places a little clumsy. E. W.

THE FOUNDATION OF MEDICAL HISTORY. By SIR D'ARCY POWER, K.B.E., F.R.C.S. (ENG.), Consulting Surgeon to St. Bartholomew's Hospital, Honorary Librarian of the Royal College of Surgeons, Etc. With an Introductory Note by WILLIAM H. WELCH. Pp. 182; 3 illustrations. Price, \$3.00.

THE foundation of the Institute of the History of Medicine at John Hopkins 3 years ago is rightly considered an event of major importance in the medical advance of this country. We may look on it as a center from which will radiate not only genial and important influences on the cultural level of physicians in general, but also in time valuable scholarly contributions to little known phases of medical history in this and other continents. In the first category belongs this first publication from the Institute, a series of 6 lectures—"pointing the way along several roads"—by last year's visiting lecturer, who is amply qualified both by his persuasive personality and by his achievements in the field of medical history to inaugurate what we hope and expect to be a "bahnbrechende" series for his country.

In the *Story of the Oldest British Hospital*, with which the author has been connected for 52 years, he tells more than enough to lead

us on to Sir Norman Moore's more complete narrative. *Dining With Our Ancestors* describes chiefly the vicissitudes of the British 3 square meals a day through the centuries. In *Biography* a deeper note is struck, being a stimulating analysis of the nature of biography, its two chief varieties and what it should and should not be. The author's long experience with the Dictionary of National Biography shines through his paragraphs. The field of *Iconography*, "the description or illustration of any object by means of drawings or figures," is illustrated by Spielman's *Vesalius* and the author's *Portraits of William Harvey*. Enough details about Lister and Paré whose "iconographies cry aloud for consideration," are given to stimulate some reader to undertake the task. In the same way in *Bibliography* interesting descriptions and analyses are used as vehicles for conveying suggestive topics to budding historians. And, finally, *Aristotle's Masterpiece* tells the story of a "hoary old debauchee" that is still to be bought in second-hand book shops. Through 427 years in which its 66 or more editions have persisted, primitive folklore, pre-Vesalian anatomy and the ever-present chicanery of pseudo-science have persisted in ministering to the itch of the prurient and in duping the ignorant—truly a lesson of value to even the most practically minded of our profession.

E. K.

THE VITAMINS. Monograph Series No. 6. By H. C. SHERMAN, Mitchill Professor of Chemistry, Columbia University, and S. L. SMITH, Senior Chemist, Office of Experiment Stations, United States Department of Agriculture. Pp. 525. Second edition. New York: The Chemical Catalog Company, Inc., 1931. Price, \$6.00.

PROGRESS in vitamin research in the 10 years since the publication of the first edition of *The Vitamins* has been so phenomenal that a second edition was imperative. In fact, so much additional material has now accumulated that the original monograph has expanded to the size of a textbook, with a bibliography of 181 pages, the titles of which alone constitute a history of investigations in this field of nutrition.

The application of quantitative methods is largely responsible for the deepening of knowledge on this important subject. While the exact chemical constitution of the vitamins has not been determined, much more is known than formerly about their chemical and physical reactions. The vitamin content of various foodstuffs and the effect upon the vitamins of exposure to the conditions to which these are subjected has been widely studied. The vitamin requirements of animals and man have also received much attention.

Further differentiation of the fat-soluble and water-soluble vitamins has added to the list of vitamins and offers the possibility of increasing their numbers. There are now 6 recognized vitamins.

The whole history of the vitamins up to 1930 is complete in this

book and is presented in such a way that not only the professional chemist to whom it is primarily addressed, but all who are interested—scientific workers, clinicians, students and other informed readers—will find helpful information in the phase of the subject that most interests them.

E. W.

THE EARLY HISTORY OF YELLOW FEVER. By HENRY ROSE CARTER, M.D., Assistant Surgeon-General (Retired), United States Public Health Service. Edited by LAURA ARMISTEAD CARTER and WADE HAMPTON FROST. Pp. 308; 5 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$5.00.

"THIS new and important study has a most interesting background. It was prepared by the late Dr. Carter, at the instance of officials of the Rockefeller Foundation, in the closing years of his life. It was known that Dr. Carter's time was limited, a restriction which indeed dictated to a degree the scope and extent of the manuscript, and it seemed necessary to record and perpetuate the contribution to the study of yellow fever which he was uniquely qualified to make. The manuscript was brought to virtual completion only at the expense of working throughout an illness severe enough to confine him to bed for long intervals, and during his last year, continuously. . . . There are many controversial questions relating to yellow fever. Many of the reports and accounts of the past are unreliable and contradictory. Much hot and bitter controversy has developed.

"Dr. Carter's manuscript attacks the problem from the viewpoint of the epidemiologic factors. These are known; the historical data are in dispute. So the work may be looked upon as, in part, an amplification and correction, or at least a testing, of the history in the light of the known epidemiology. Thus many of the historical questions may be settled definitely. If, for instance, yellow fever is reported as continuing for a term of years under conditions which render continuance impossible, it is known that the disease could not have been yellow fever.

"Quite as much epidemiology and bacteriology as history is therefore presented. Dr. Carter wrote from first-hand information and this, coupled with the unusual approach to the problem, results in a study of particular point and value."

After consideration of the epidemiology of yellow fever (46 pages) and diseases which may have been confused with it (32 pages) the author goes at length into the various sites that might be regarded as its place of origin. He concludes that both biologic and historical evidence, without being conclusive, point strongly to its African origin. Though Dr. Carter died in 1925, and considerable water has flowed through the mill since that time, this book should long retain its interest and value.

E. K.

BOOKS RECEIVED.

NEW BOOKS.

- Man and Medicine.* By DR. HENRY E. SIGERIST, Professor at the University of Leipzig. Introduction by DR. WILLIAM H. WELCH, Professor of the History of Medicine, The Johns Hopkins University. Translated by MARGARET GALT BOISE. Pp. 340. New York: W. W. Norton & Co., Inc., 1932. Price, \$4.00.
- The Story of Medicine.* By VICTOR ROBINSON, M.D., Professor of History of Medicine, Temple University School of Medicine, Philadelphia. Pp. 527. New York: Albert and Charles Boni, 1931. Price, \$5.00.
- Cytology and Cellular Pathology of the Nervous System.* Three volumes. By various contributors. Vol. I: *Neurones, Nerve Sheaths and Nerve Endings.* Vol. II: *Neuroglia, Microglia, Blood Vessels, Meninges, Pineal, Pituitary, Eye.* Vol. III: *Neoplasms, Malformations, Reactions.* Pp. 1280; 886 illustrations, 15 in color. New York: Paul B. Hoeber, Inc., 1932. Price, \$30.00.
- Italian Medicine.* Vol. VI of *Clio Medica.* By ARTURO CASTIGLIONI, M.D., Professor of the History of Medicine, Royal University of Padua, Italy. Translated by E. B. KRUMBHAAR, M.D., Professor of Pathology, University of Pennsylvania. Pp. 134; 11 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, \$1.50.
- Biochemistry in Internal Medicine.* By MAX TRUMPER, Ph.D., Clinical Chemist and Toxicologist, Jefferson Medical College and Hospital, and ABRAHAM CANTAROW, M.D., Instructor in Medicine, Jefferson Medical College. With a Foreword by ELMER H. FUNK, M.D., Sutherland M. Prevost Professor of Therapeutics at Jefferson Medical College. Pp. 454; 11 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$5.50.
- The Cambridge Medical School.* By SIR HUMPHRY DAVY ROLLESTON, BART., G.C.V.O., K.C.B., M.D., HON. D.Sc., D.C.L., LL.D., Regius Professor of Physic in the University of Cambridge, etc. Pp. 235; illustrated. New York: The Macmillan Company, 1932. Price, \$5.00.
- Intracranial Tumors.* By HARVEY CUSHING, Professor of Surgery, Harvard Medical School; Surgeon-in-Chief, Peter Bent Brigham Hospital, Boston. Pp. 150; 111 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$5.00.
- Man and Microbes.* (A Century of Progress Series.) By STANHOPE BAYNE-JONES, M.D., Professor of Bacteriology, School of Medicine and Dentistry, University of Rochester. Pp. 128, 17 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, \$1.00.
- The Wisdom of the Body.* By WALTER B. CANNON, M.D., Sc.D., LL.D., George Higginson Professor of Physiology, Harvard Medical School. Pp. 312; 41 illustrations. New York: W. W. Norton & Co., 1932. Price, \$3.50.
- A Text-Book of Human Physiology.* By AUGUST KROGH, Ph.D., LL.D., Professor of Zoöphysiology in Copenhagen University, Copenhagen. Revised and Edited by KATHERINE R. DRINKER, A.B., M.D., Formerly Research Assistant in Applied Physiology, Harvard Medical School, Boston. Pp. 233; 108 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$2.75.
- Abstracts, Proceedings of Meetings of the New York Pathological Society,* held November 19 and December 17, 1930; January 22, February 26, March 26, April 23 and May 28, 1931. Reprinted from Archives of Pathology. Pp. 56; 2 illustrations.

Publications of the Committee on the Costs of Medical Care. No. 13. *A Survey of the Medical Facilities of the State of Vermont*. By ALLON PEEBLES, PH.D. Pp. 70. Price, \$1.50. No. 15. *Midwives, Chiropodists, and Optometrists*. By LOUIS S. REED, PH.D. Pp. 321; 97 tables. Price, \$1.00. Chicago: The University of Chicago Press, 1932.

The White House Conference Publications on Child Health and Protection. New York: The Century Company, 1932. *Growth and Development of the Child. Part III. Nutrition*. Report of the Committee on Growth and Development, KENNETH D. BLACKFAN, M.D., Chairman. Pp. 532; various tables and charts. Price, \$4.00. *Obstetric Education*. Report of the Subcommittee on Obstetric Teaching and Education, FRED LYMAN ADAIR, M.D., Chairman. Pp. 302; various tables and charts. Price, \$3.00.

NEW EDITIONS.

Clinical Atlas of Blood Diseases. By A. PINEY, M.D., M.R.C.P., Director of Pathological Department, The Cancer Hospital, London; Consulting Pathologist, Chelmsford Hospital, and STANLEY WYARD, M.D., M.R.C.P., Physician, The Cancer Hospital, London, and Princess Beatrice Hospital. Pp. 105; 38 illustrations, 34 in color. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1932. Price, \$4.00.

One of the best of these atlases that has come to our attention. If not misunderstood as replacing text-books, these little books have important uses.

A *Text-book of Psychiatry*. By D. K. HENDERSON, M.D. (EDIN.), F.R.F.P.S. (GLAS.), Physician-Superintendent, The Glasgow Royal Mental Hospital, and R. D. GILLESPIE, M.D. (GLAS.), M.R.C.P., D.P.M., (LOND.), Physician for Psychological Medicine, Guy's Hospital, London. Pp. 595. Third edition. New York: Oxford University Press, 1932. Price, \$4.50.

A new chapter on the Psychiatry of Childhood is given excellent treatment and the inclusion of a brief survey of the United States laws governing mental diseases is helpful. No superior to this volume has been written in English in our opinion.

Medical Formulary. By E. QUIN THORNTON, M.D., Assistant Professor of Materia Medica in the Jefferson Medical College, Philadelphia. Pp. 352. Thirteenth edition revised. Philadelphia: Lea & Febiger, 1932. Price, \$2.50.

Keeps well up to date in the wilderness of new remedies that are constantly being brought out.

Manual of Bacteriology. By ROBERT MUIR, M.A., M.D., Sc.D., LL.D., F.R.S., Professor of Pathology, University of Glasgow, and The Late JAMES RITCHIE, M.A., M.D., F.R.C.P. (EDIN.), Late Irvine Professor of Bacteriology, University of Edinburgh. Revised by CARL H. BROWNING, M.D., D.P.H., F.R.S., Gardiner Professor of Bacteriology, University of Glasgow, and THOMAS J. MACKIE, M.D., D.P.H., Irvine Professor of Bacteriology, University of Edinburgh. Pp. 866; 212 illustrations, 6 color plates. Ninth edition. New York: Oxford University Press, 1932. Price, \$4.75.

A concise treatment covering a very extended field. Illustrations and practical procedures are included. S. M.

Applied Pharmacology. By A. J. CLARK, M.C., M.D., F.R.C.P., F.R.S., Professor of Materia Medica and Pharmacology in the University of Edinburgh. Pp. 590; 72 illustrations, 50 tables. Fourth edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1932. Price, \$4.00.

This well-known work has been brought up to date by the incorporation of material dealing with recent advances in the fields of vitamins, endocrines, vegetative nervous system, circulator regulation, etc. Its viewpoint is more physiological than is the case with other English and American texts on pharmacology. C. S.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Pellagra: Analysis of 102 Cases.—The present study (BOGGS and PADGET, *Bull. Johns Hopkins Hosp.*, 1932, 50, 21) is based upon the observations of the senior author in the medical service of the Baltimore City Hospital for a period of 20 years. The discussion of the disease, pellagra, calls attention to a classification of pellagra which seems to the authors to be rather clearly defined: (a) Simple pellagra; (b) post-alcoholic variety, and (c) pellagra arising as a complication of some other disease. In the first group there were 31 cases, in the second group 40, and in group three 31. The onset of the pellagrous lesions was not characteristic of the seasonal peak observed in the South in early spring. Most of the patients on admission complained of dermatitis; diarrhea was next in frequency, as an entering complaint, and sore mouth was third. One-fifth of the patients were admitted with complaints unassociated with pellagrous lesions. The patients with a history of having used alcohol to excess present the most interesting problem. Of the 40 cases, 36 when they entered the hospital had been on a spree lasting from 4 to 6 weeks, while the 4 had for long periods taken a daily ration of distilled liquor. The further statistical study of these cases as a whole showed that the skin lesions were present on the dorsum of the hand in each case. Stomatitis was present in three-fourths of the cases, as was the diarrhea. Forty-five per cent of the patients had involvement of the spinal cord, lesions of which resemble subacute combined sclerosis with a tendency toward involvement of the posterior columns. Apparently the degree of involvement was not marked. One-half of the patients showed some type of psychosis. An anemia was found in 80 per cent. Ninety per cent of cases showed an absence of free hydrochloric acid when this examination was carried out. In the treatment of this group as a whole, the most satisfactory results were obtained with a liver diet. Without the liver diet 69 per cent of the patients died. On a liver diet approximately 20 per cent succumbed. The recovery figures correspond with the rate for death. The central nervous system symptoms apparently were not affected to any very great extent by the liver feeding. The question of why there should be any association between alcoholism and pellagra has arisen. The authors write that

three theories suggest themselves to explain this relationship: first, that the pellagra is dependent upon the presence of some deleterious element in the alcoholic drink; second, that it may depend upon simple withdrawal of food, but this does not explain it, as many of these people still take large quantities of alcohol daily and yet eat their customary ration, nor does the hypothesis that there may be some toxic substance in the alcohol afford a satisfactory answer, as the sources of the alcohol are too varied to suggest a constant type of poisoning. The third theory seems to be the likely one. Either the alcohol destroys the pellagra-preventive factor in the gastrointestinal tract or the gastrointestinal tract is so altered by the alcohol that it is incapable of assimilating the pellagra-preventive factor. This latter assumption would seem to be the correct answer to the enigma. It would explain also the pellagra which develops in cachectic states. While the authors do not mention this fact, it would seem likely that this explanation affords a solution of the paradox in which the severely ill pellagrin, despite adequate diet, continues to go down hill. It would seem in these cases that the gastrointestinal tract is so altered, probably by the pellagra itself, that the pellagrin is unable to make use of the factor which might prevent progress of the disease.

SURGERY

UNDER THE CHARGE OF

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The Union of Grafts of Live and Preserved Fascia With Muscle.—HAAS (*Arch. Surg.*, 1931, 23, 571) says that dead, preserved fascia lata united with muscle, just as rapidly and as firmly as did live fascia lata. The union of both dead and live fascia depended mainly on the ingrowth of the endomysium and perimysium. The muscle cells themselves appears to be transformed into elements of fibrous tissue and to aid in the uniting process. There was some evidence that the preserved fascia lost some of its elasticity and stirred up more reaction in the surrounding tissue than did live fascia. Dead, preserved fascia may be used clinically for union with a muscle, but it seems advisable to utilize the fascia, if possible, because the latter appears to be transformed into tendinous tissue more readily.

Some Angiospastic Syndromes in the Extremities.—MORTON AND SCOTT (*Ann. Surg.*, 1931, 94, 839) say that the increased interest in the peripheral vascular diseases has focused attention especially on the lesions associated with spasm of the vessels. This is a natural reaction, because it is in this group that therapeutic relief can be looked for more hopefully in a large proportion. There are several types of angiospasm, which can be recognized and separated into major groups as follows: (a) In organic vascular disease; (b) idiopathic paroxysmal (Raynaud's) disease; (c) dependent upon organic or functional nervous diseases; (d) consecutive to trauma; (e) venospasm. In Raynaud's disease the funda-

mental abnormality is a hypersensitivity of the peripheral arteries to cold. However, vasoconstrictor impulses play an important rôle by initiating and accentuating many of the attacks. Consequently the advisability of removing the sympathetic innervation can be determined by the effect of regional anesthesia in releasing the spasm during an attack. Organic and functional nervous disorders frequently are accompanied by an accentuated vasoconstrictor tone locally. Trauma in the extremities may be followed by an arterial spasm, frequently associated with pain. This is probably due to vasoconstrictor impulses induced by reflex afferent stimuli from the traumatized area. The authors believe that such a reaction is a fundamental response incident to trauma and scar formation. There is an individual variation in the degree of manifestation of this reaction and it may be present as a latent hypersensitivity to cold. Evidence has been presented that angiospasm affecting principally veins occurs as a clinical entity.

THERAPEUTICS

UNDER THE CHARGE OF

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AND

SOMA WEISS, M.D.,

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The Copper Content of Human Milk and of Cow's Milk.—In contrast to potassium, sodium, calcium and magnesium, no physiologic rôle has been ascribed to the traces of aluminum, copper, manganese, vanadium and zinc which are found in the animal body. Copper has only recently been shown to have a constant level in the blood stream. Steenbock demonstrated that white rats underfed with cow's milk show arrested growth and an anemia which can be cured only by the administration of copper salts. This experiment suggests that cow's milk is poor in copper. ZONDEK and BANDMAN (*Klin. Wchnschr.*, 1931, 10, 1528) investigated the comparative copper content of human and cow's milk. Eighty-five samples of human milk and 90 of cow's milk were analyzed by the Warburg method. The human milk was uniformly richer in copper. The cow's milk contained traces of copper so slight that they could not be demonstrated with the Warburg method but only with the Ashing process. The average copper content of the cow's milk was 0.15 to 0.2 mg. per liter; and that of the human milk 0.5 to 0.6 mg. per liter. No definite change in the copper content was observed at different periods of lactation. An infant fed on cow's milk usually receives the milk doubly diluted, and as the water is practically copper free, the copper concentration is reduced by half. All the foodstuffs used in the formula are poor in copper. Anemia among infants who are artificially fed is probably more common than is realized. Copper prophylaxis among artificially fed infants therefore is rational.

Histamin in the Treatment of the Rheumatoid Diseases.—Mature consideration of the various remedial measures which have proved more or less effective in the relief of pain in the rheumatoid affections leads DEZSÖ DEUTSCH (*Med. Klin.*, 1931, 27, 1491) to the conclusion that their therapeutic actions have the common characteristic of producing hyperemia in the skin or muscles, or both, of the affected region. On the basis of the demonstrations by Lewis and others that mechanical, thermal and other procedures causing hyperemia do so by the local liberation in the tissues of histamin, the author sought to employ this agent directly. He finds that the subcutaneous or intramuscular injection of histamin is capable of producing a local vasodilatation which is accompanied by considerable amelioration of pain and relaxation of muscle spasm. The injection methods, however, are associated with unpleasant general histamin reactions which render their therapeutic use unsatisfactory. He finds, however, that it is possible to introduce satisfactory quantities of histamin locally into the tissues by cataphoresis. Controlled observations show that the electrical current applied exerts no beneficial action. He has investigated the results of this method of treatment in some 250 cases and finds that in the majority the pain and muscle spasm are both relieved promptly, usually temporarily, even by the first treatment. The conditions responding most satisfactorily are myalgia, arthritis deformans and chronic polyarthritis. Sciatica does not respond but pseudosciatica, which seems to be due primarily to muscle spasm yields promptly to treatment. Although periosteal pain may be diminished in about half the cases, the relief is purely transitory. The observation of outstanding interest is that histamin cataphoresis produces relief more rapidly than does any other procedure. It is a fact also that it seems to be potent in a great many conditions in which relief is difficult to obtain by any other therapeutic procedure.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Physical Analysis of the Adolescent Problem.—TODD (*Am. J. Dis. Child.*, 1932, 43, 533) states that the reproductive function presupposes an organism substantially fully developed. Consequently, although the general broad lines of sexual development were established very early in the process, the reproductive organs lie fallow for a long period of time, during which growth of the body and adaptation of response are developed before Nature returns to the completion of her task. In contrast with the rapidity of attainment by lower mammals of bodily maturity is the relative tardiness of primate development. Actual bulk is of secondary importance. A relatively long early childhood and rapid adolescence are characteristic of all primates except man, who takes from the sixth to the twentieth year to accomplish the development which is covered by the anthropoid in 2 years. What Nature does well she does quickly, but at the cost of considerable

strain on the organism. The dangers to life in the adolescent anthropoid are reduced to difficulties to mere disordered progress in the long-attenuated adolescence of man. A long adolescent period maintains a plastic state of accumulation and registration of experiences before the human organism crystallizes into maturity. The human brain is substantially adult in pattern at 6 years. Thereafter mental development is dominated by finer discriminations of judgment trained by experience. Hence adolescence is characterized by mental, rather than by physical, complexities. Since adolescence is but a phase of childhood on the threshold of maturity, it falls into the scope of the pediatrician rather than of the internist. The supposed individual variations in date of inception and in sequence of expression of the phenomena of adolescence are to be attributed to the interplay of factors, mainly internal and endocrine in origin, the combination and precise significance of which are still to be defined. Intimately bound up with these is the progress to maturity of the skeleton, the adolescent features of which, such as date and velocity of epiphyseal union, act as a register of progress. On a single examination they give a definition of status serial or periodic roentgenographic examinations of the skeleton provide a measure of progress. This physical expression is not an academic finding but an exceedingly important indicator of constitutional health or defect and may be applied with confidence in the assessment of developmental growth.

Dried Lactic Acid Milk as a Long-continued Diet for Infants.—HESS and ROBINS (*J. Am. Med. Assn.*, 1932, 98, 1250) made this comparative feeding study with the idea of evaluating the effect on growth and development of infants following long-continued feeding with dried lactic acid milk. With special regards to rickets they offer the following observations: Of the 18 breast-fed infants 1 showed mild clinical rickets between the fifth and ninth months. Roentgenograms in this case were negative. Only 5 of the babies were on breast feeding exclusively for a period longer than 25 weeks. This partly accounts for the low percentage of cases of rickets recorded in the breast-fed group. Of the 8 breast-fed infants in whom the breast feeding was later complemented by Merrell-Soule powdered lactic acid milk 2 had mild rickets, with positive Roentgenograms in 1, and 1 had moderate rickets with considerable bone change. In the 2 infants showing rickets by Roentgen rays the one with considerable bone change was on breast and complement to the age of 16 weeks, after which she was on Merrell-Soule dried lactic acid milk for the following 5 months. The second infant showing moderate bone changes had been on breast milk complemented by Merrell-Soule for 15 weeks and received the Merrell-Soule dried milk for the following 4 months. This infant, the only one in the entire group of 85 cases showing any considerable bone changes, had a moderate case of eczema and a diarrhea developed which required hospitalization for a period of 2 weeks during the fifth month. In the 7 infants in whom breast feeding was complemented with Mead Johnson dried lactic acid milk mild clinical rickets with slight bone changes developed in 2 and in another there was a moderate clinical rickets. None of these showed roentgenographic evidence of bone change. Of the 5 infants on fluid cultured lactic acid milk mild

clinical rickets developed with slight bone changes in 1 and moderate clinical rickets without Roentgen evidence in 1. Of 5 infants on sweet cow's milk plus U. S. P. lactic acid mild clinical rickets with slight bone changes developed in 1. Of 30 infants on dried Merrell-Soule lactic acid milk 6 showed mild clinical rickets and 1 of these slight bone changes. These 30 infants were all fed dried lactic acid milk from the third week of life, and 20 of these were on this feeding for 6 months or longer and 12 of them remained on this diet throughout their eighth month. Of the entire group of 85 cases only 1 showed marked bone changes. This is the one mentioned above who had eczema and an attack of diarrhea that required hospitalization. Rickets was evidenced clinically in mild degree in 13 of the cases, and in 3 cases it was of moderate degree. Of these 4 showed slight Roentgen changes and the one mentioned before showed marked changes. Of the 30 infants on dried lactic acid milk for periods of from 5 to 9 months, dated from the third week of life, only 6 showed mild clinical rickets and only 1 of these showed slight bone changes in Roentgenograms. The clinical results indicate that dried lactic acid milks can be used under the same conditions as cultured lactic acid milk and cow's milk plus U. S. P. lactic acid.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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FRANK B. BLOCK, M.D.,

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Regeneration of Uterine Mucosa After Delivery.—In what was probably the last contribution to the literature by the late J. WHITRIDGE WILLIAMS (*Am. J. Obst. and Gynec.*, 1931, 22, 664) he has presented a most complete and interesting study of the regeneration of the uterine mucosa during the puerperium, more particularly in relation to the changes occurring at the placental site. These observations are based upon the study of a large series of uteri removed by supravaginal amputation following Cesarean section, as well as a certain number obtained at autopsy upon women dying from other causes than infection during the first 3 days of the puerperium, and upon others removed by operation during that period, but especially upon a series of 18 uteri obtained by supravaginal amputation at various periods throughout the puerperium. He states that his study has demonstrated that the regeneration of the placental site is in no way connected with an inflammatory change, that there is no indication of any extensive necrotic process and that all of the specimens show unusual proliferation of endometrial tissue, which does not merely cover the surface of the placental site, but invades it in all directions, but particularly extends between it and the underlying muscularis, so that in a general way it undermines the placental site and ultimately leads to its extrusion

or exfoliation. The most important evidence is presented by a uterus 48 days after delivery, in which the placental site is represented by a tag of tissue, 1 by 3.5 mm., projecting into the uterine cavity, but still attached by its base to the superficial portion of the endometrium. The high-power section of this tissue shows that the stroma of the polypoid mass presents the histologic structure which is characteristic of the placental site.

Cancer Grading in Relation to Prognosis.—In the past few years much interest has been shown in the relation of the maturity of the cells in a cancer to the prognosis from the clinical aspect, many pathologists being of the opinion that the relationship is a very definite one. As REIMANN (*Ann. Surg.*, 1931, 94, 381) states, however, there are two types of grading, namely, according (1) to prognosis, and (2) to Roentgen ray sensitivity and there is much confusion about the subject on this account. The first type of grading attempts to forecast end-results while the second type predicts whether or not a tumor will be destroyed by irradiation. He believes that the former cannot be done while the latter can be accomplished with a considerable degree of accuracy. The reason why he believes that prognostic tumor grading cannot be done is because a microscopic section of the tumor will not show how completely the surgeon removed the tumor. Moreover, the microscopic appearance of most tumors varies in different parts sufficiently to influence the grading. He therefore refuses to grade tumors, especially biopsy material because he believes that the surgeon might be inclined to do a less radical operation than should be done if a tumor is considered to be of low malignancy. We must realize that tumors, if malignant, even of the slowest growth, will kill the patient if given time and if not completely removed. In a general way, the less differentiated the cells of a tumor, the more sensitive they are to irradiation, but here again if the patient is to receive irradiation, the radiologist should give all the treatment that is possible without regard to the sensitivity of the constituent tumor cells and of course without causing damage to the surrounding healthy tissues. From Reimann's viewpoint therefore, this subject is of academic interest but should have no influence on the extent of treatment which should always be as much as the patient can tolerate.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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AND

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Exophthalmos in Infantile Scurvy.—DUNNINGTON (*Arch. Ophthalm.*, 1931, 6, 731) reports a case of unilateral exophthalmos which appeared suddenly in a girl aged 7 months. Eleven days before examination,

sudden swelling of the left upper lid and bulging of the left eye occurred in the course of a slight "head cold." The swelling practically disappeared in 3 days but recurred 4 days later. The left upper lid was markedly swollen, ecchymotic and tender to touch. The eye was proptosed about 2 mm. and was pushed downward and outward. Upward rotation was limited. The eye itself was normal. The child's legs were tender to touch. The upper gums were spongy and bleeding and the lower slightly ecchymotic. A few small ecchymotic spots were present in the skin of the buttocks. Examination of the nose and roentgenograms of the accessory sinuses did not reveal any pathology. Roentgenograms of the long bones revealed changes characteristic of scurvy. Three ounces of orange juice was added to the daily diet and the swelling of the upper lid and the proptosis disappeared in 4 days. Exophthalmos appears as a complication of scurvy usually only in infants. The average age of the patients in the 22 authentic reported cases is $10\frac{1}{2}$ months, the youngest being 7 months and the eldest 2 years. Kruckow reported 1 case of recurrent orbital hemorrhage in an adult with scurvy. Operative and necropsy findings have established that the cause of the proptosis is extravasation of blood between the orbital plate of the frontal bone and the subjacent periosteum. The tendency to hemorrhage in scurvy is explained by the increase in permeability of the bloodvessel walls as a result of a defect in the cement substance of the endothelial cells produced by lack of vitamin C in the diet. Hart and Lessing, Harden and Zilva, and Zilva and Still have noted hemorrhages into the orbit in experimental scurvy in monkeys. These hemorrhages absorbed spontaneously but recurred unless antiscorbutic treatment was instituted. The hemorrhages in infants tend to absorb rapidly, the time, in the cases reported since 1912, varying from 4 days to 1 month. The hemorrhages do not calcify. The exophthalmos may be slight or sufficient to endanger the cornea unless operative interference is instituted. The fact that, in scurvy, subperiosteal hemorrhage is prone to occur at the site of rapid physiologic growth explains the tendency to hemorrhagic extravasation at the upper inner angle of the orbit. However, Dunnington believes that orbital hemorrhage is less frequent than is suggested in textbooks on pediatrics in which exophthalmos is stated to occur in 10 per cent of the cases of infantile scurvy. Hemorrhages may also occur in the lids, conjunctiva, anterior chamber and retina.

RADIOLOGY

UNDER THE CHARGE OF

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The Postpneumonic Lung.—Chronic lung changes following pneumonia depend on the degree to which the various tissues of the lung are involved by the acute process and the severity of the injury which they

sustain. Among the most important of the pneumonias likely to result in chronic changes, says HART (*Am. J. Roentgenol. and Rad. Therap.*, 1931, 26, 371), are influenzal pneumonia, influenzal pneumonia invaded by streptococci, the bronchopneumonias accompanying measles and pertussis, and Friedländer's pneumonia. The pneumonic process may take any of three possible courses: (a) The exudate may be absorbed and recovery ensue; (b) the exudate may become organized and fibrotic changes and chronic nontuberculous infection develop, or (c) suppuration may occur. If either of the two latter possibilities eventuate, chronic terminal conditions may be expected. These may take the form of bronchiectasis, chronic nontuberculous infections, abscess formation, or fibrosis, either localized or diffuse. Systematic follow-up and periodical roentgenologic examinations of patients in whom resolution does not take place promptly would throw much light on chronic post-pneumonic lesions.

The Use of Opaque Oils in the Diagnosis of Maxillary Sinus Disease. The injection of opaque oil into the maxillary antrum enables a roentgenologic demonstration of pathologic conditions and, according to BEELER, SMITH and COLLINS (*Am. J. Roentgenol. and Rad. Therap.*, 1931, 26, 302) determines better than any other means the proper type of treatment. The oil can be injected without harmful effects, although there is usually a reaction of the mucous membrane which lasts until the oil is extended. The authors use lipiodol diluted one-third in olive oil; their results with brominol and campiodol have also been good. The normal antrum, when injected, will show a thin line of separation about 1 mm. wide between the oil and the sinus wall. At the base the prominences over the tooth roots may be apparent as smooth curves. Polypi produce a smooth localized defect in the shadow. Cysts and mucocoeles produce a similar defect but somewhat larger and more circumscribed. Hyperplastic changes cause an irregular outline.

NEUROLOGY AND PSYCHIATRY

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Convulsive Seizures, Their Production and Control, With Special Reference to the Probable Mechanism of the Seizure Itself.—FAY (*Am. J. of Psychiat.*, 1931, 10, 551) believes that a direct relationship between fluid intake, its storage and elimination, and major convulsive attacks has been clinically and experimentally established. A rational means of definite fluid balance has also been determined. The results have justified the conclusion that the major forms of the convulsive state are superadded phenomena associated with hydration and disturbed

water metabolism. Convulsive seizures may be regarded as representing a normal mass reaction of the motor areas after inhibitory centers have been depressed or released by specifically applied pressure, anoxemia or exhaustion. In the series of cases studied the grand mal attacks have gradually receded into Jacksonian or petit mal manifestations as dehydration was accomplished. The petit mal seizures have increased in severity and the zone of response widened as fluids and intracranial pressure has been increased. The assumption is justified that the stimulus capable of producing a petit mal or Jacksonian attack at one time finds a wide field of application and permits a generalized cortical release when inhibitory factors have been removed by pressure secondary to hydrated states.

Biochemical Changes During Emotion.—JANKOWSKA (*L'Encephale*, 1931, 26, 204) examined hyperemotional patients to see what biochemical changes were associated with variations in emotional state. It was found impossible to examine the blood chemistry owing to the constant emotional disturbance caused by the prick of the needle. The urine was therefore examined for hourly quantity, reaction (pH), chlorid, nitrogen, ammonia nitrogen and sometimes for calcium. As a general rule it was found that during emotion there was a tendency to alkalinity, expressed as a rise in pH from the normal (5 to 6) to between 6 and 7, or even slightly above this. This was associated with an increase in total nitrogen and in quantity, and sometimes also in calcium and ammonia. In a case of permanent anxiety high figures were obtained in each of these examinations throughout the patient's stay in hospital. In 2 cases of schizophrenia variations in the urine similar to those found during emotion were observed, without the display of any emotion by the patient. Two possible explanations of this were offered: (1) That schizophrenics experienced emotions which they did not betray, or (2) that the changes in the urine were due to functional disturbances in the brain which in normal subjects led to the somatic expression of emotions.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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On the Microscopic Histology of Experimental Tuberculosis in Different Species.—FELDMAN (*Arch. Path.*, 1931, 11, 896) with the use of pure cultures of the tubercle bacillus of human, bovine and avian origin, using the subcutaneous intraperitoneal, intravenous and intracerebral routes of inoculation, induced experimental tuberculosis in guinea pigs, rabbits, chickens and dogs. From the lesions obtained, the author made a comparative study to determine whether the anatomic character of the cellular reaction in the respective species varied with the type of the tubercle bacillus used to incite the lesions,

or whether the histologic character of the lesions in a given species was constant, regardless of the form of the tubercle bacillus present, and concluded that the histologic nature of tuberculous infection in a given species is essentially the same, regardless of the form or the origin of the particular strain of the tubercle bacillus responsible for the lesions. Variations in the character of the reaction of the tissues to the tubercle bacillus are not determined by the type of the organism *per se*, but by certain factors which are inherent in the species possessing the infection. The guinea pig and dog developed disseminated tuberculosis after intracerebral inoculation with the avian strain. In the common fowl infection was obtained locally in the brain with human and bovine types and all tuberculous lesions possess certain anatomic characters (focal circumscribed collections of monocytic or epithelioid cells, or a rather large, clear type, which are multiple and often become confluent, and even though a conglomerate tubercle results, the separate follicle-like masses of epithelioid cells is usually maintained and is discernible) which distinguish them from tuberculous lesions with the same bacteria in lower mammals. The histologic nature of tuberculous infection in a given species is essentially the same, regardless of the form or the origin of the particular strain of the tubercle bacillus responsible for the lesions. The author concluded that it would be injudicious to designate a given tuberculous infection as being due to any of the three types of the tubercle bacillus, without comparative pathogenicity tests, the histology being of no particular value for determining the types.

Total Occlusion of the Right Branch of the Pulmonary Artery by an Organizing Thrombus.—A case showing total occlusion of the right branch of the pulmonary artery by a large thrombotic mass, which had undergone advanced organization was reported by MEANS and MALLORY (*Ann. Int. Med.*, 1931, 5, 417). The degree of organization suggested that the thrombus had been present for weeks or months. The patient, who was diagnosed clinically as a case of hypertensive and arteriosclerotic heart disease, had shown symptoms of cardiac insufficiency for a year prior to his death with marked cyanosis during the last few days of life, but presented no history in any way suggestive of pulmonary embolism or thrombosis. No abnormal physical signs were found in the right lung before death. At autopsy this lung showed no evidence of necrosis, scarring or collapse, and while it was slightly smaller and less crepitant than the opposite lung, was air containing throughout. A greatly hypertrophied bronchial artery and two large arteries which were traced upward along the sides of the trachea into the neck and which had probably arisen from the inferior thyroid arteries, had established a collateral circulation. Microscopically the alveoli were empty or contained a mucoid secretion, the capillaries being difficult to make out. The epithelium of the alveolar walls showed evidence of metaplasia to a high cuboidal or low columnar type. The authors believe that a medium sized embolus may have produced a partial occlusion of the pulmonary artery, gradually growing, however, until total occlusion had occurred, time being allowed for a rich anastomotic channel to be formed. The case is of interest in illustrating that such a gross disturbance, if occurring slowly need produce no damage to lung or give rise to any abnormal findings on physical examination.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 18, 1932

The Rôle of Intensity and Duration in the Stimulation of Single End Organs in the Eye.—H. KEFFER HARTLINE (from the Eldridge Johnson Foundation for Medical Physics, University of Pennsylvania). In the stimulation of the eye by light it is necessary to consider both the total quantity of energy in the stimulating light and the intensity of this energy. These two factors were studied in preparations of the eye and optic nerve of the horseshoe crab, *Limulus*, in which the discharge of impulses in a single fiber of the optic nerve was recorded oscillographically. Such a single fiber preparation shows that there is a threshold of intensity below which no impulses are discharged no matter how large the total amount of energy may be which enters the eye over a long period of time. Above this threshold the effect of intensity is to increase the frequency of the discharge and to decrease the initial latent period. For long exposures (over 1 second) a steady state is reached in which a constant inflow of energy results in a steady output of nerve impulses at a frequency determined only by the intensity.

For short exposures (less than 0.1 second) it is the total energy of the flash of light which chiefly determines the resulting discharge. The frequency of discharge, the total number of impulses and the velocity of the latent period are all increased by increasing the energy of the flash, whether this be done by increasing duration or intensity. The reciprocity law (Bunsen Roscoe) holds in the first approximation.

The relation between logarithm of the energy of flash and maximum frequency of discharge is linear, up to a limiting duration which is slightly less than the latent period. Above this limiting duration the frequency is determined by intensity only. Velocity of latent period and total number of impulses discharged parallel this behavior closely.

Absorption of Glucose From the Colon.—WALTER W. EBELING (from the Laboratory of Surgical Research, University of Pennsylvania). Considerable difference of opinion exists among investigators as to whether glucose in appreciable amounts can be absorbed from the large bowel. A study of glucose absorption from the intestinal tract of the normal, the pancreatectomized and the insulinized dog was outlined in which were controlled factors which had previously not been taken into consideration.

Glucose solutions are absorbed at a very slow rate when placed in the entire colon of the dog. Hypertonic solutions (10 per cent) are absorbed very little faster than are isotonic solutions. When a marked glucose deficit occurs in the blood glucose can be absorbed from the colon approximately as rapidly as it can from a low ileal loop of the noninsulinized dog. The presence of glucose in the solution in the colon causes a retardation in the rate of water absorption. The total

amount of glucose which can be administered and absorbed from the colon under the very best conditions would appear to be too small for any considerable therapeutic effect.

Studies on Bone Growth as Seen in the Transparent Chamber Introduced Into Rabbit's Ear.—HENRY T. KIRBY-SMITH (from the Laboratory of Anatomy, University of Pennsylvania). In order to study the growth and absorption of bone the rabbit's ear method of tissue study was utilized. Six-day endosteal callus obtained from the radius was placed in the chamber at the time of its insertion into the ear.

Thirty-nine days after transplantation two small oval masses of homogeneous refractile material with lacunæ and canaliculæ—all characteristic of bone—had appeared on the table of the chamber. The chamber space was about $45\ \mu$ thick and daily microscopic observations were made at high magnifications. The bone mass watched most intensively was 0.36 mm. long, 0.26 mm. wide and about 0.04 mm. thick. After a slight extension on one side it entered a quiescent phase until the forty-eighth day, when absorption of the bone was first noted. The absorption continued and an excavated area appeared near one end leaving a thin shell of bone at the edge of the bone mass. On the seventy-fifth day the edge of this thinned-out portion broke away leaving a semilunar space between the bone fragment and fibrous tissue on one hand and the parent bone on the other. During the second day after the fracture nongranular oval cells and fibers could be seen in the semilunar space. In the region between the fragment and the parent bone the fibers were irregularly arranged. Up to the fifth day following the fracture the essential changes were an increase in the fibers and their grouping into larger bundles in the interstices of which were clear spherical cell-like bodies. On the sixth day following the fracture these irregular fibers were found to be infiltrated with highly refractile granules which were coarser near the parent bone and finer at the periphery. On the seventh day the granules had begun to fuse and on the ninth day they formed a homogeneous refractile material which surrounded nearly all the cells in the fibrous matrix. The tempo of this growth corresponds very closely with the series of events which follows injury to the rabbit's ulna or radius.

The thin bone spicule which had broken away from the parent bone remained unchanged for 5 days. On the sixth day an excavated area appeared on its lower end, in which was seen a finely granular protoplasmic mass containing clearer round areas with dark centers. Observations over a period of 7 hours showed marked diminution in the size of the spicule, absorption occurring only in the region of the protoplasmic mass. The process of absorption consisted of first a disappearance of the highly refractile material leaving a fibrous substance which in turn disappeared. No refractile material or fibers were seen in the protoplasmic mass. Eight days after the fracture the isolated spicule had completely disappeared.

There was no change in the bloodvessel pattern and no marked change in the circulation during the process of growth or absorption.

A New Type of Transparent Chamber for Studying the Effect of Chemicals Upon Living Tissues.—R. G. ABELL and E. R. CLARK (from the Laboratory of Anatomy, University of Pennsylvania). In the

extension of the types of chambers for insertion in the rabbit's ear a chamber was desired by means of which it would be possible to study with the high powers of the microscope a very thin layer of living tissues while these tissues were being subjected to the action of chemical solutions of known and desired composition. Such a chamber has now been developed and is known as the "moat" chamber. The moat chamber, which is a modified "bay" chamber, is composed principally of glass and mica, and contains a very thin, transparent, inclosed space called the bay. Living tissues grow into the bay through two small entrance holes at one end, and then across it toward the opposite end, which opens into a much larger inclosed space, called the moat. Chemical solutions can be injected into the moat by means of two silver access cannulæ, and subsequently sealed within it. Such solutions diffuse into the bay, and there come in contact with the living tissues. Owing to the fact that the bay has a glass bottom and a mica top, and a depth of approximately only 50 micra, the cellular details of the tissues can be clearly seen with the oil-immersion lens, and the effect upon them of experimentally introduced chemical solutions studied with the microscope.

Ten to 15 days after the insertion of the moat chamber connective tissue, bloodvessels and in some cases lymphatic vessels grow into the bay. Chemical studies can be begun at this time, previous to it or at a later date. Such studies can be made for a period of several days or weeks, or, if desired, for several months.

Preliminary experiments have shown that the growth of the tissues in the bay is not disturbed by the injection of sterile Ringer solution into the moat, and that a dye, such as methylene blue, when placed in the moat passes to the region of living cells and tissues.

The moat chamber affords an opportunity to study the effect of the tissues growing in the bay upon the chemical solutions placed in the moat, as well as the effect of such chemical solutions upon the tissues. Such solutions can be withdrawn from the moat at any time and their gain, loss or change analyzed.

By means of the moat chamber access may be had to the intercellular space without mechanical disturbance to the tissues themselves. Effects produced by chemicals experimentally introduced into this space can be studied microscopically.

The Use of the Chick Embryo as a Pharmacologic Test Object.—EDITH M. HALL (introduced by F. S. HAMMETT) (from The Lankenau Hospital Research Institute, Philadelphia). A determination of the response of cardiac muscle to physiologic and pharmacologic agent is obviously a desideratum in any study of bodily processes. Moreover, when chemical means of assay of products of biologic or therapeutic significance are unavailing then standardization must be had by the use of responsive biologic test objects. The present report is an investigation into the reaction of the heart of the chick embryo to digitalis and its suitability for the assay of this drug.

Embryos of 72 to 76 hours' incubation, having 26 to 32 somites, and a posterior vitelline vein, 9 to 12 mm. in width, were used *in situ* in the opened egg kept at 40° C.

Preliminary tests with a digitalis leaf infusion brought out that 10 minims is the most favorable volume for injection under the chorion and that with appropriate dilutions the medium period of from 45 to 75 minutes for complete cardiac inhibition is the best for drug activity.

Using these standards, it was possible to assay the action of various digitalis tinctures kindly supplied by the McNeil Company. The values obtained satisfactorily approximated those of the official frog heart method with the same preparations. The dilutions used for the chick embryo heart in terms of that effective in the frog are as follows:

1. Approximately 10 minims of a 1 per cent infusion of normal U. S. P. digitalis leaf shall stop embryo chick heart in medium period of 45 to 75 minutes.

2. 0.06 cc. of 1 per cent infusion of normal U. S. P. digitalis leaf for each gram of frog weight shall stop the heart in systole for 1 hour.

Repeated tests with the same dilution of the same tincture give the same result within 0.5 per cent. Dilutions of the same tincture give comparable results.

The results obtained with this method are expressions of the action of the drug on cardiac musculature alone, since neural control is not yet in force in embryos of this stage of development. It is possible that the procedure offers opportunity for differentiating those alkaloids of the digitalis group specifically effective in cardiac muscle and those which also exert a reaction on the neuromuscular mechanism as a whole.

Authors' Acknowledgment.

"By an oversight, an acknowledgment of help from the Josiah Macy, Jr., Foundation was overlooked in submitting our recent article 'Metabolic Studies in Addison's Disease,' 1932, 183, 1. At a critical stage of the investigations of Swingle and Piffner on the cortical hormone of the adrenal glands, they received generous aid from the Josiah Macy, Jr., Foundation. This made possible the continuation of their work, and enabled us to carry on our studies. We wish with deepest appreciation to acknowledge this aid." L. G. ROWNTREE and CARL H. GREENE.

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